User Guide for Micro, Small and Medium-sized Enterprises (SMEs)

on the administrative and procedural aspects of the provisions, laid down in Regulation (EC) No 726/2004, that are of particular relevance to SMEs

© 2009 EMEA

DOCUMENT HISTORY

INITIAL RELEASE FOR CONSULTATION	December 2006
REVISED VERSION RELEASED FOR CONSULTATION (Incorporating new text in Section 5 and comments on other Sections)	December 2007
CONSULTATION (Deadline for comments)	March 2008
FINAL VERSION (Updating Sections: 3.3 on Advanced Therapies and Technologies; 4.5 on Orphan Medicines and Paediatrics; 6.6 on e-CTD and Annex I)	October 2008
FINAL VERSION (Updating Annex I - National provisions for SMEs applicable to the pharmaceutical sector: change of contact point for BfArM, Germany	April 2009

© EMEA 2009

TABLE OF CONTENT

1. INTRODUCTION 4

1.1 OBTAINING A MARKETING AUTHORISATION WITHIN THE EUROPEAN UNION 5
1.2 OVERVIEW OF (DATA) REQUIREMENTS FOR OBTAINING MARKETING AUTHORISATION IN THE EU 7
1.3 EU LEGISLATIVE FRAMEWORK FOR PHARMACEUTICALS 7

2. SME INITIATIVE 9

2.1 OBJECTIVE 9
2.2 DEFINITION OF AN SME 9
2.3 INCENTIVES FOR SMES (EU PROVISIONS AND NATIONAL PROVISIONS) 10
2.4 ROLE OF THE SME OFFICE 12
2.5 HOW TO REQUEST SME STATUS 12

3. SCIENTIFIC ADVICE 14

3.1 SCIENTIFIC ADVICE/PROTOCOL ASSISTANCE 14
3.2 SCIENTIFIC GUIDELINES AND POSITION PAPERS 16
3.3 ADVANCED THERAPIES AND TECHNOLOGIES 16

4. MEDICINAL PRODUCT DEVELOPMENT (HUMAN) 18

4.1 QUALITY 19
4.2 NON-CLINICAL DEVELOPMENT 23
4.3 CLINICAL DEVELOPMENT 25
4.4 GMP/GCP/GLP 28
4.5 MEASURES FOR ORPHAN MEDICINES AND PAEDIATRICS 29

5. MEDICINAL PRODUCT DEVELOPMENT (VETERINARY) 34

5.1 MAXIMUM RESIDUE LIMITS (MRL) 34
5.2 QUALITY 35
5.3 SAFETY 35
5.4 EFFICACY 36
5.5 IMMUNOLOGICALS 37
5.6 GMP/GLP/GCP 37

6. APPLICATION FOR CENTRALISED MARKETING AUTHORISATION 38

6.1 ACCESS TO THE CENTRALISED PROCEDURE 38
6.2 SELECTION OF RAPPORTEUR/CO-RAPPORTEUR 38
6.3 (INVENTED) NAME OF PRODUCTS EVALUATED VIA THE CENTRALISED PROCEDURE 39
6.4 EMEA CONTACT POINT IN THE CENTRALISED PROCEDURE 40
6.5 EMEA PRE-SUBMISSION MEETING 40
6.6 COMPILATION OF THE APPLICATION DOSSIER 41
6.7 SUBMISSION AND VALIDATION OF THE APPLICATION DOSSIER 42
6.8 EVALUATION OF THE APPLICATION 42
6.9 RE-EXAMINATION OF THE CHMP/CVMP OPINION 44
6.10 DECISION-MAKING PROCESS 44
6.11 EARLY ACCESS TO THE EU MARKET 45
6.12 MARKETING OF THE MEDICINAL PRODUCT IN THE COMMUNITY 47
6.13 RISK MANAGEMENT AND PHARMACOVIGILANCE 47

7. OTHER USEFUL INFORMATION 49

7.1 INFORMATION ON MEDICINAL PRODUCTS 49
7.2 LIST OF ABBREVIATIONS 50
7.3 CONTACT POINTS AT THE EMEA 51

ANNEX 1 52

© EMEA 2009

1. Introduction

This guide has been prepared for micro, small and medium-sized enterprises (SMEs) operating in the pharmaceutical sector. Its aim is to facilitate understanding of the main aspects of medicinal product legislation. The guide is structured to follow the chronological stages of developing a medicinal product. An overview of the scientific data requirements for obtaining a marketing authorisation in the European Union (EU) is provided. The regulatory procedures in place to optimise development and obtain an EU marketing authorisation are also summarised.

The guide focuses primarily on the requirements for authorising innovative medicinal products for human or veterinary use. The guide is not intended to be an exhaustive document but rather to raise SMEs' awareness of the various more detailed sources of information available, with links throughout the text to additional information.

In December 2005, Commission Regulation (EC) No 2049/2005[1] introduced provisions aimed at promoting innovation and the development of new medicinal products for human and veterinary use by SMEs. This guide is intended to fulfil the obligation laid down in Article 12 of that Regulation, which calls for a 'User Guide' on the administrative and procedural aspects of medicines legislation that are of particular relevance to smaller companies to be published by the European Medicines Agency (EMEA).

Pursuant to the SME regulation, companies can access financial assistance (in the form of fee reductions and fee deferrals) and administrative assistance from the agency, details of which are outlined in Section 2 of this guide. To facilitate contact with the agency, an 'SME Office' was launched in December 2005 and is dedicated to addressing the particular needs of smaller companies.

Any feedback on the content or format of this guide should be forwarded to the SME Office (smeoffice@emea.europa.eu).

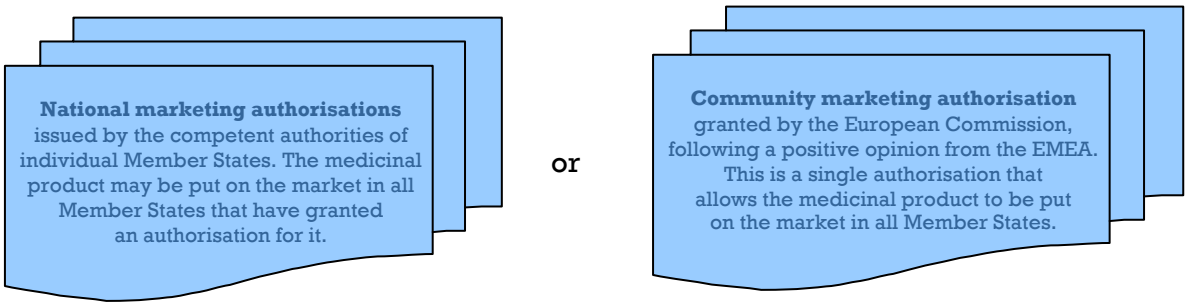
[1] *Official Journal L 329, 16/12/2005 pp. 4-7.*

© EMEA 2009

1.1 Obtaining a marketing authorisation within the European Union

Prior to marketing a medicinal product in the EU, a marketing authorisation (product licence) must be obtained. The company responsible for placing the medicinal product on the market (so-called marketing authorisation holder) must be "established"[2] within the EEA (Iceland, Liechtenstein, Norway and the Member States of the European Union).

In the EU, there are two types of marketing authorisation:


National marketing authorisations
issued by the competent authorities of individual Member States. The medicinal product may be put on the market in all Member States that have granted an authorisation for it.
or
Community marketing authorisation
granted by the European Commission, following a positive opinion from the EMEA. This is a single authorisation that allows the medicinal product to be put on the market in all Member States.

Approved conditions of use are laid down in the summary of product characteristics[3] (prescribing information for health professionals), the labelling and the package leaflet for users[4].

This user guide will focus on the use of the centralised procedure for obtaining a Community marketing authorisation. Further information on the regulatory routes for obtaining national marketing authorisations, namely the mutual recognition and decentralised procedure, are highlighted in Section 1.1.2 below. Applicants are advised to refer to the Notice to Applicants, Volume 2A and Volume 6A – Procedures for marketing authorisation[5], for more detailed information.

1.1.1 Community marketing authorisation – the centralised procedure

The European Medicines Agency coordinates the existing scientific resources of the Member States in to evaluate and supervise medicinal products for both human and veterinary use throughout the European Union. The EMEA is primarily involved in the centralised procedure for obtaining a Community marketing authorisation.

For queries relating to: orphan designation, paediatric investigation plans, pan-European scientific advice, filing an application for marketing authorisation through the centralised procedure, and EudraVigilance, the EMEA is the primary point of contact.

If an SME has any doubt about the appropriate point of contact for a particular issue, the SME Office can provide assistance: smeoffice@emea.europa.eu

The agency also gives scientific advice to research-based companies in the development stage of new medicinal products (see Section 3.1) and develops guidelines on quality, safety and efficacy testing requirements (see Section 3.2).

---

[2] Being established, here, means having a permanent legal structure (formed in accordance with the law of an EU Member State or other EEA country) that allows the concerned person to assume the duties and responsibilities as well as to perform the tasks laid down by Community law, see Annex II of Chapter I, Vol. 2A (human medicines) or 6A (veterinary medicines) of the Notice to Applicants http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/index.htm .

[3] In accordance with Article 11 of Directive 2001/83/EC for human medicines and Article 14 of Directive 2001/82/EC for veterinary medicines.

[4] In accordance with Articles 54, 55, 59 and 63 of Directive 2001/83/EC for human medicines and Articles 58-61 for veterinary medicines.

[5] Published on the European Commission's Pharmaceuticals website: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/eudralex_en.htm

© EMEA 2009

The centralised procedure is mandatory for certain types of medicinal products and optional for others. Medicinal products made of recombinant proteins, veterinary medicinal products intended primarily for use as performance enhancers, human medicinal products containing a new active substance for treatment of acquired immune deficiency syndrome, cancer, neurodegenerative disorders, diabetes, viral diseases, auto-immune diseases/other immune dysfunctions, and designated orphan medicinal products fall within the mandatory scope and must be filed centrally at the EMEA.

The centralised procedure is optional for products containing new active substances for indications other than those stated above and for products which constitute a significant therapeutic, scientific or technical innovation, or products for which the granting of a Community authorisation would be in the interest of patients or animal health at Community level. It is also optional for immunological veterinary medicinal products for the treatment of animal diseases that are subject to EU prophylactic measures. Applicant companies should confirm eligibility for evaluation through the centralised procedure with the EMEA at least 7 months prior to submitting the centralised marketing application (see Section 6.1).

In order to obtain a Community authorisation, an application should be submitted to the EMEA. The scientific evaluation of the application is carried out by the Committee for Medicinal Products for Human Use (CHMP) or Committee for Medicinal Products for Veterinary Use (CVMP) of the EMEA, and a scientific opinion is prepared. The opinion is sent to the European Commission, which drafts a decision and, having consulted the Member States through the relevant Standing Committee, adopts the decision and grants a marketing authorisation.

Such a marketing authorisation is valid throughout the Community and confers the same rights and obligations in each of the Member States as a marketing authorisation granted by that Member State.

The centralised procedure is briefly detailed in Section 6 of this Guide. Chapters 4 and 6 of Volume 2A of the Notice to Applicants[6] should be consulted for further information.

1.1.2 National marketing authorisations – mutual recognition & decentralised procedures

Each Member State of the European Union, Iceland, Liechtenstein and Norway has its own national authority(ies) responsible for regulating medicinal products for human and veterinary use. These authorities have a common website called the Heads of Agencies website[7] that serves as a useful connection point to the websites of individual authorities.

Sponsors with queries relating to: regulatory approval for the conduct of clinical trials, national scientific advice, manufacturing authorisations, filing an application for marketing authorisation nationally, through the mutual recognition or decentralised procedure, reporting of adverse events, or pricing and reimbursement matters, are advised to contact the relevant national competent authority.

The authorities of the Member States are responsible for granting marketing authorisations for medicinal products placed on their markets, with the exception of medicinal products subject to Community marketing authorisations. If a company seeks a national marketing authorisation, an application must be submitted to the competent authority of the Member State concerned. If a company is seeking a national marketing

[6] Published on the European Commission's Pharmaceuticals website: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/eudralex_en.htm
[7] Heads of Agencies website address: http://heads.medagencies.org/

© EMEA 2009

authorisation in more than one Member State, the mutual recognition or decentralised procedure are available to facilitate the granting of harmonised national authorisations across Member States. Chapter 2 of Volume 2A of the Notice to Applicants should be consulted for further information.

1.2 Overview of (data) requirements for obtaining marketing authorisation in the EU

An application for marketing authorisation for a new medicinal product for human use must generally be accompanied by the particulars and documents set out in Article 8(3) and Annex 1 of Directive 2001/83/EC[8]. The requirements include data generated from pharmaceutical (physicochemical, biological or microbiological) tests, non-clinical (toxicological and pharmacological) tests and clinical trials, evaluation of the potential environmental risks posed by the medicinal product, as well as a detailed description of the pharmacovigilance system and, where appropriate, of the risk-management system which the applicant will introduce (see Sections 4.1-4.3 and 6.13). For medicines developed for use in children there is a requirement to agree a paediatric investigation plan early in development (see Section 4.5.2).

Article 12(3) and Annex I to Directive 2001/82/EC[9], as amended, list the requirements for the individual sections of the dossier that needs to be submitted as part of the application for authorisation of a veterinary medicinal product.

An overview of the key issues to be addressed in the development of medicinal products for human use and veterinary use are outlined in Section 4 and 5 of this guide respectively.

1.3 EU legislative framework for pharmaceuticals

All EU legislative texts are published in the Official Journal of the European Union (OJEU) in all official EU languages[10]. For sponsors unfamiliar with the EU legislative process, a useful starting point is the overview of the hierarchy of Community texts given in Chapter 1, Annex I of Volumes 2A (human) and 6A (veterinary) of the Notice to Applicants.

Commission Regulation 2049/2005 of 15 December 2005 introduces provisions for SMEs.

Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004, as amended, is the legal base for the **centralised procedure** for the authorisation and supervision of human and veterinary medicinal products and the establishment of the European Medicines Agency (EMEA).

Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on **orphan medicinal products**, (which entered into force on 22 January 2000), introduces provisions to stimulate the development of medicinal products for patients suffering from rare diseases.

Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006, as amended on **medicinal products for paediatric use**.

Directives 2001/82/EC and 2001/83/EC of the European Parliament and of the Council of 6 November 2001, as amended, lay down the **Community code** relating to medicinal products for veterinary use and human use respectively.

Council Regulation (EEC) No 2377/90 of 26 June 1990, as amended, lays down a Community procedure for the establishment of **maximum residue limits** for veterinary medicinal products in foodstuffs of animal origin.

[8] *Official Journal L 311, 28/11/2004 pp. 67-128.*
[9] *Official Journal L 311, 28/11/2001 pp. 1-66.*
[10] Legislation published in the OJEU can be found via the EUR-Lex website: http://eur-lex.europa.eu/

© EMEA 2009

The above-mentioned Directives and Regulations are available in the EudraLex section[11] of the European Commission's Pharmaceuticals website. These legislative texts — together with Directives 2001/20/EC and 2005/28/EC on Good Clinical Practice (in the conduct of clinical trials on human medicinal products and as regards investigational products for human use respectively), and Directives 2003/94/EC and 91/412/EEC on Good Manufacturing Practice (for human medicinal products and veterinary medicinal products respectively) — form the legislative backbone of medicinal product regulation in the EU.

The Notice to Applicants facilitates the interpretation and application of the Community pharmaceutical legislation, and should be consulted by any potential applicant. It is not legally binding, and in case of doubt about legislative requirements, companies should always refer to the legal texts themselves.

[11] EudraLex: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/

© EMEA 2009

2. SME Initiative

2.1 Objective

The primary aim of the SME initiative is to promote innovation and the development of new medicinal products by smaller companies. It is hoped that this will be achieved by providing incentives to help SMEs overcome the main financial and administrative hurdles associated with pre-marketing authorisation procedures, particularly scientific advice, marketing authorisation application and inspection procedures.

2.2 Definition of an SME

In determining which companies are eligible for SME incentives, the EMEA applies the EU definition of micro, small and medium-sized enterprises provided in Commission Recommendation 2003/361/EC[12]. This means that companies are classified according to their category (autonomous, partner or linked) and size (micro, small or medium), as defined below:

AUTONOMOUS ENTERPRISES*
My enterprise holds less than 25% (capital or voting rights) in another and/or another holds less than 25% in mine.
** Note: there are exceptions for certain types of investors. See Article 3(2)(D) in the Annex of Commission Recommendation 2003/361/EC.*

PARTNER ENTERPRISES
My enterprise holds at least 25%, but no more than 50% in another and/or another holds at least 25%, but no more than 50%, in mine.

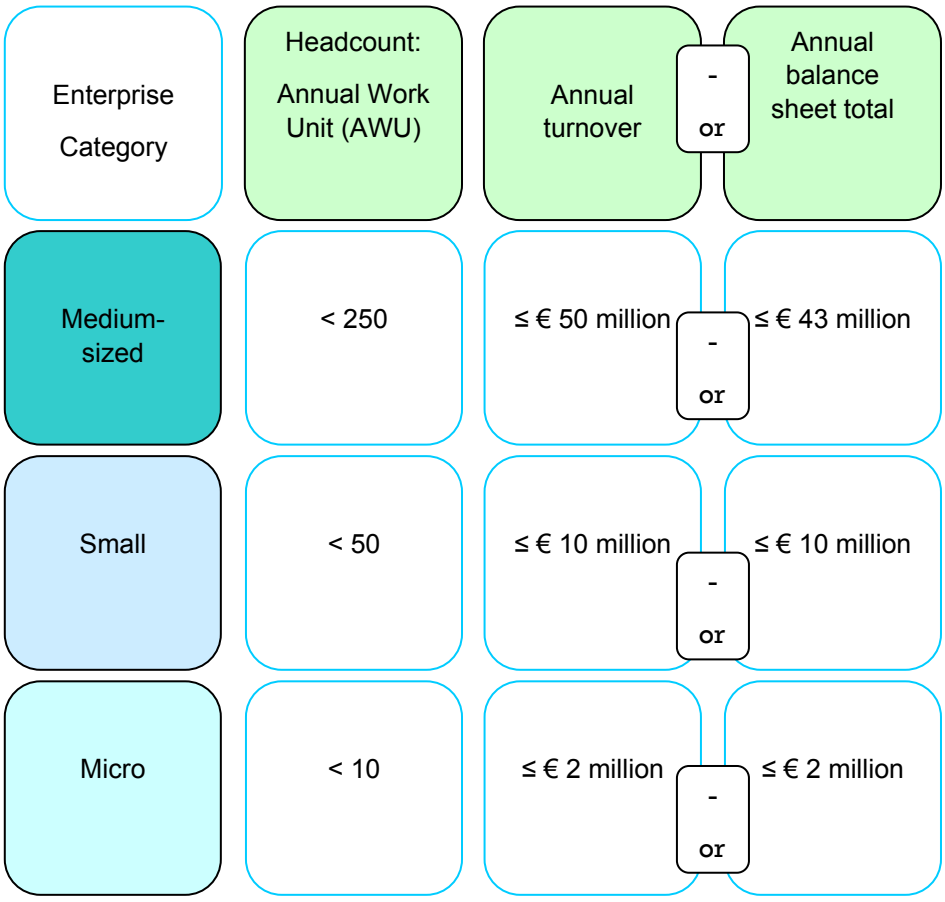
LINKED ENTERPRISES
My enterprise holds more than 50% of the shareholders' or members' voting rights in another and/or another holds more than 50% in mine.

Depending on the category in which the enterprise fits, some or all of the headcount and financial data from other partner or linked enterprises may need to be counted when calculating whether the SME criteria are met.

[12] Commission Recommendation 2003/361/EC :
http://eur-lex.europa.eu/LexUriServ/site/en/oj/2003/l_124/l_12420030520en00360041.pdf

© EMEA 2009

SME Thresholds (Commission Recommendation 2003/361/EC)



The information above has been extracted from 'The new SME definition - User guide and model declaration'[13], published by the European Commission, which provides further information on the definition of an SME.

2.3 Incentives for SMEs (EU provisions and national provisions)

2.3.1 Incentives offered by the EMEA

Incentives

The EU incentives offered by Regulation (EC) No 2049/2005 apply equally to the human and veterinary sectors, and include:

- Regulatory, administrative and procedural assistance from the EMEA's SME Office;
- Fee reductions for scientific advice, inspections and (for veterinary medicines) establishment of maximum residue limits;
- Fee exemptions for certain administrative services of the EMEA;
- Deferral of the fee payable for an application for marketing authorisation or related inspection;
- Conditional fee exemption where scientific advice is followed and a marketing authorisation application is not successful;
- Assistance with translations of the product information documents submitted in the application for marketing authorisation.

[13] http://ec.europa.eu/enterprise/enterprise_policy/sme_definition/sme_user_guide.pdf

© EMEA 2009

SMEs operating in the pharmaceutical sector are often innovative companies that can notably benefit from the pooling of scientific expertise at EU level. The SME initiative has been designed, with a substantial 90% fee reduction for scientific advice, to encourage SMEs to seek advice from the EMEA on all issues relating to the development of new medicinal products, with a view to maximising the chances of a successful marketing authorisation (see Section 3.1 for information on scientific advice).

Other financial incentives include a 90% fee reduction for any Good Manufacturing Practice (GMP), Good Clinical Practice (GCP) or Good Laboratory Practice (GLP) inspection requested by the EMEA, and the possibility to request deferred payment of the inspection fee. For veterinary medicines, there is also the possibility to request a 90% fee reduction for establishment of maximum residue limits. Full fee exemptions are also offered for administrative services from the EMEA (e.g. EMEA certificates of medicinal products).

In the run up to filing an application for marketing authorisation, the fee payable to the EMEA for review of the application may place financial constraints on smaller companies. For SMEs, fee payment may now be deferred by up to 45 days after the date of notification of the centralised marketing authorisation, or, in the event of withdrawal of the application, within 45 days of the date of notification of withdrawal. In the event of a negative outcome, where scientific advice has previously been sought from the EMEA and taken it into account in the development of the medicinal product, the fee for the application for marketing authorisation will be fully waived by the agency.

Because translating product information into all EU languages represents a considerable financial and administrative burden to SMEs entering the EU market, the EMEA will provide for translation into all EU official languages of product information documents (summary of product characteristics, conditions of the marketing authorisation, label and package leaflet) submitted in the application for a Community marketing authorisation. It will be the responsibility of the applicant SME to provide the Norwegian and Icelandic translations.

Access to financial or administrative assistance from the EMEA under the SME initiative is subject to the company's SME status remaining valid at the time that their application or request is validated by the Agency. Fee reductions and fee deferrals must be requested in advance of any submission. Further information on fee reductions/deferrals and how to request them is available in the document 'Fee reductions/deferrals for micro, small and medium-sized enterprises (SMEs)' (EMEA/366526/2005)[14].

2.3.2 Other EU incentives for SMEs

Further information on the whole spectrum of EU policies, legislation, programmes and initiatives relevant to Europe's SMEs is available from the European Commission through its European Portal for SMEs[15].

2.3.3 National provisions for SMEs

Article 12 of Commission Regulation (EC) No 2049/2005 requires the SME User Guide to reference existing national provisions for SMEs, applicable to the pharmaceutical sector. These are provided in Annex 1.

[14] http://www.emea.europa.eu/pdfs/SME/36652605en.pdf
[15] European Portal for SMEs: http://ec.europa.eu/enterprise/sme/index_en.htm

© EMEA 2009

If companies have a query relating to any existing national provision and would like to contact the national competent authority in question, contact points are also provided in Annex 1.

2.4 Role of the SME Office

The SME Office was established at the EMEA to offer assistance to SMEs who, due to lack of experience with the centralised authorisation procedure or lack of familiarity with the EMEA and its procedures, may otherwise experience difficulties with the development and marketing of their new medicinal products. The SME Office will facilitate contacts with the relevant scientific and regulatory staff within the Agency to address any questions that may arise during development of a medical product, particularly in the run up to submitting a marketing authorisation application

2.5 How to request SME status

2.5.1 Assignment of SME status

Companies wishing to benefit from SME incentives should visit the SME Office section of the EMEA website[16] first. Before requesting financial or administrative assistance from the Agency, companies should complete the form 'Declaration on the qualification of an enterprise as a micro, small or medium-sized enterprise (SME)'[17]. This should be submitted to the SME Office, together with the most recent annual accounts (audited if possible) for the applicant enterprise and any linked or partner enterprise, the proof of establishment of the organisation in the Community (taken here to mean an EU Member State, Iceland, Liechtenstein or Norway), and details of upstream (i.e. owners of your enterprise's shares or voting rights) and downstream ownership structure (i.e. your enterprise's participation in other companies in terms of shares or voting rights) in the form of e.g. an overview chart of the company structure. If your enterprise is newly established and does not have finalised financial reports, estimates should be provided for the reference period declared.

Companies are strongly recommended to read 'The new SME definition – User guide and model declaration'[18], published by the European Commission, before completing the form. It is particularly useful in helping to determine whether the applicant company is an autonomous, partner or linked enterprise, and whether it is necessary to complete the annexes to the declaration form.

If the documentation appears to be in order and no clarification is required, the EMEA will issue the enterprise with an EMEA-SME number. At that point the company may request access to the incentives offered by the SME regulation. The agency reserves the right to request further information from the company to establish that the SME criteria are met and may, at any time, perform audits as part of its SME programme. The applicant enterprise will be liable to consequences in case of a false declaration.

2.5.2 Maintenance of SME status

A company's SME status will expire two years after the date of closure of the accounts on which the declaration has been based. In order to extend SME status, companies are

[16] http://www.emea.europa.eu/SME/SMEoverview.htm
[17] EMEA/366649/2005: http://www.emea.europa.eu/pdfs/SME/36664905en.doc
[18] http://ec.europa.eu/enterprise/enterprise_policy/sme_definition/sme_user_guide.pdf

© EMEA 2009

advised submit an updated SME declaration form (duly signed) for the company, a copy of the latest audited annual accounts for the applicant enterprise and any linked or partner enterprises, together with updated information on the upstream and downstream ownership of the companies declared. This information can be submitted to the EMEA as soon as it is available, or, at the latest, three months prior to the expiry date. The EMEA does not send out individual reminders for renewal.

3. Scientific Advice

3.1 Scientific advice/Protocol assistance

At any stage of development, and irrespective of eligibility to use the centralised procedure for marketing authorisation, sponsors can request scientific advice from the EMEA.

SMEs are particularly encouraged to initiate an early dialogue with the agency, in the form of scientific advice. This helps the sponsor to ensure that the appropriate tests and studies are performed, so that no major objections regarding the design of the tests are likely to be raised during evaluation of the marketing authorisation application. Such major objections can significantly delay the marketing of a product, and, in certain cases, may result in refusal of the marketing authorisation. Following the Agency's advice, therefore, increases the probability of a positive outcome.

For human medicinal products, scientific advice is given by the EMEA's Committee for Medicinal Products for Human Use (CHMP) on the recommendation of the Scientific Advice Working Party (SAWP-H). For veterinary products, it is given by the Committee for Medicinal Products for Veterinary Use (CVMP) on the recommendation of the veterinary equivalent, the SAWP-V.

Guidance on how to put together a request for scientific advice for human medicinal products[19] and veterinary medicinal products[20] is available from the EMEA. Detailed information on how to apply, including a template for notifying intent of submission, submission deadlines and details of the programme for EMEA-FDA parallel scientific advice are available on the EMEA website.

The agency offers assistance to applicants in putting their scientific advice requests together through free pre-submission meetings. SMEs are strongly recommended to request a pre-submission meeting or teleconferences at the time they notify their intent to file the request.

Scientific advice is restricted to purely scientific issues. Regulatory requests should be the subject of separate advice from the EMEA.

3.1.1 Scope of scientific advice

Scientific advice may be sought on the tests required to support an application for marketing authorisation for a medicinal product (see Sections 4.1-4.3 and Sections 5.1-5.5) in the areas of:

- quality (chemical, pharmaceutical and biological testing);
- non-clinical/safety (toxicological and pharmacological tests);

[19] 'EMEA guidance for companies requesting scientific advice (SA) and protocol assistance (PA)' (EMEA/H/4260/01): http://www.emea.europa.eu/pdfs/human/sciadvice/426001en.pdf

[20] 'EMEA guidance for companies requesting scientific advice' (EMEA/CVMP/17329/2004-Rev.2): http://www.emea.europa.eu/pdfs/vet/sciadvice/17232904en.pdf

© EMEA 2009

- clinical aspects (clinical safety and efficacy);
- the establishment of MRLs for veterinary medicinal products.

Scientific advice for designated orphan medicinal products (applies to medicinal products for human use only. See Section 4.5.1) is called 'protocol assistance' and, in addition to the above, may include questions relating to:

- demonstration of significant benefit within the scope of the designated orphan indication;
- issues addressing similarity/clinical superiority in case other potentially similar orphan medicinal products have market exclusivity in the concerned therapeutic indication.

Guidance on how to seek protocol assistance for designated orphan medicinal products is also available on the EMEA website[20].

For veterinary medicinal products, scientific advice requests may include questions relating to limited markets (including minor uses and minor species (MUMS) applications).

Sponsors can also request advice from the EMEA on innovative methods or drug development tools for medicinal products for human use through a new, voluntary qualification process[21]:

- qualification advice on the acceptability of a specific use of the proposed method (e.g. use of a biomarker) in a research and development (R&D) context (non-clinical or clinical studies), based on the assessment of submitted data;
- scientific advice on future protocols and methods for further method development towards qualification, based on the evaluation of the scientific rationale and on preliminary data submitted.

3.1.2 Fee reductions for scientific advice

The scientific advice procedure attracts a fee, which varies depending on the scope of the advice. This may deter some companies from seeking advice early on in development, or from making several successive requests. Therefore, access for SMEs to the Agency's scientific advice has been facilitated with a substantial 90% fee reduction. Furthermore, as the scientific evaluation of a marketing authorisation application is more likely to be favourable where scientific advice has been sought from the Agency, in the event of a negative outcome, a conditional exemption of the fee for the application for marketing authorisation will be given to applicants who have requested such advice and who have actually taken it into account in the development of their medicinal product. Further information on the level of fee reductions/deferrals available to SME applicants and how to request them is available in the document 'Fee reductions/deferrals for micro, small and medium-sized enterprises (SMEs)' (EMEA/366526/2005).

For designated orphan medicinal products, scientific advice (or so-called protocol assistance) is free of charge. The agency also provides free advice on the development of medicinal products for paediatric use.

In order to support the research and development of veterinary medicinal products for minor species and for rare indications in animals, a programme of free scientific advice for such products has been initiated by CVMP. Requests for free scientific advice under

[21] http://www.emea.europa.eu/htms/human/mes/biomarkers.htm

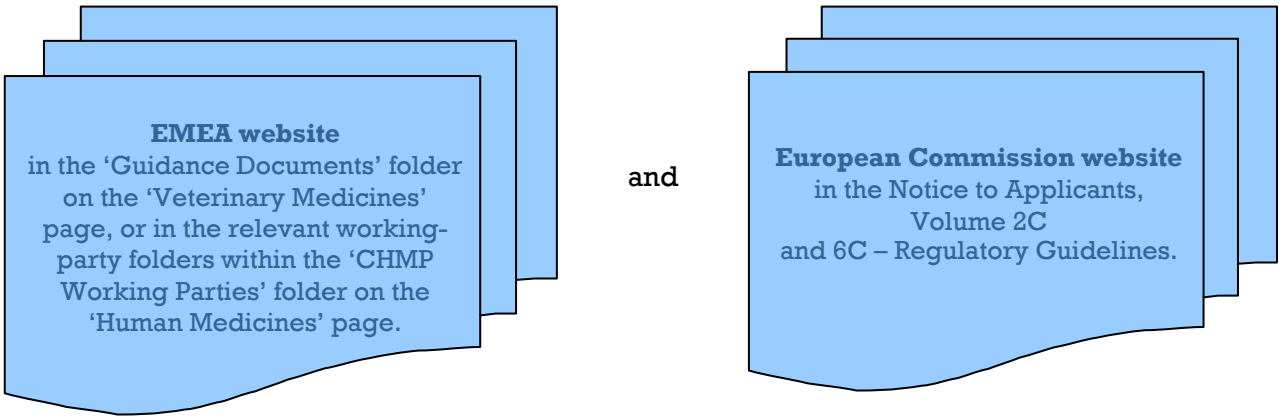
© EMEA 2009

this initiative, and in accordance with the published criteria[22], should be sent to CVMP for a decision on the granting of the fee waiver. Scientific advice may also be requested on reduced data requirements, with corresponding reduced fees, for veterinary medicinal products considered to be MUMS products in accordance with the adopted CVMP guidelines (quality, safety, efficacy and immunologicals).

3.2 Scientific guidelines and position papers

The EMEA has streamlined the presentation of scientific guidelines for human and veterinary medicinal products on its website[23]. This compilation supersedes the publication of guidelines for medicinal products by the European Commission in the Eudralex Volumes 3 and 7 that had been previously supplemented with further publications or revisions on the EMEA website.

Documents which do not fall under the heading of scientific guidelines, such as historical position papers, question-and-answer documents, or general regulatory guidelines can be found on the:


EMEA website
in the 'Guidance Documents' folder on the 'Veterinary Medicines' page, or in the relevant working-party folders within the 'CHMP Working Parties' folder on the 'Human Medicines' page.
and
European Commission website
in the Notice to Applicants, Volume 2C
and 6C – Regulatory Guidelines.

3.3 Advanced therapies and technologies

New legislation governing the development and authorisation of advanced therapy medicinal products (ATMPs) - Regulation (EC) No 1394/2007 [24] of the European Parliament and of the Council of 13 November 2007 - was adopted on 13 November 2007 and will apply in the European Union as of end of 2008. Three kinds of products are defined by the new legislation: gene therapy, somatic cell therapy and human tissue engineering.
The overall aim of the new legislation is to ensure a high level of scientific evaluation of these medicinal products and facilitate their EU market access by patients. A new EMEA Committee, the Committee for Advanced Therapies (CAT) will commence work in December 2008. New tasks and responsibilities for the agency include the following provisions:

- Opinion to the CHMP on the quality, safety and efficacy of ATMPs
- Certification of quality/non-clinical data of ATMP developed by SMEs.

---

[22] 'General criteria for granting free scientific advice in respect of supporting the research and development of veterinary medicinal products destined for MUMS' (EMEA/CVMP/1136/03):
http://www.emea.europa.eu/pdfs/vet/sciadvice/113603en.pdf
[23] Scientific guidelines for human and veterinary medicinal products:
http://www.emea.europa.eu/htms/human/humanguidelines/background.htm
http://www.emea.europa.eu/htms/vet/vetguidelines/background.htm
[24] *Official Journal L 324, 10/12/2007 pp. 121-137.*

© EMEA 2009

- Scientific recommendation on medicinal product classification.

Further information relating to EU legislation on advanced therapies and its implementation is available on the EMEA website and on the European Commission's Pharmaceuticals website[25].

SMEs developing ATMPs can approach the agency through the SME office or the Innovation Task Force (ITF). The activities of the ITF include ATMPs, but also other emerging therapies and technologies.

One of ITF objectives is to establish a platform for early informal dialogue with companies, particularly SMEs, to proactively identify scientific, legal and regulatory issues. To this end, SMEs may request a briefing meeting with the ITF to discuss legal, regulatory or scientific issues for selected product(s) in their pipeline. These may be organised in cooperation with specialised EMEA Committees/Working Parties. In addition, the ITF can provide regulatory advice to applicants on the eligibility for access to EMEA procedures (such as scientific advice and the centralised procedure for marketing authorisation) as a medicinal product e.g. when there are uncertainties as to whether a product would qualify as a medicinal product.

Further information on how to contact the ITF, including forms for requesting briefing meeting and eligibility to EMEA procedures, is available on the EMEA website[26]. General queries can be sent to the ITF secretariat: **ITFsecretariat@emea.europa.eu**

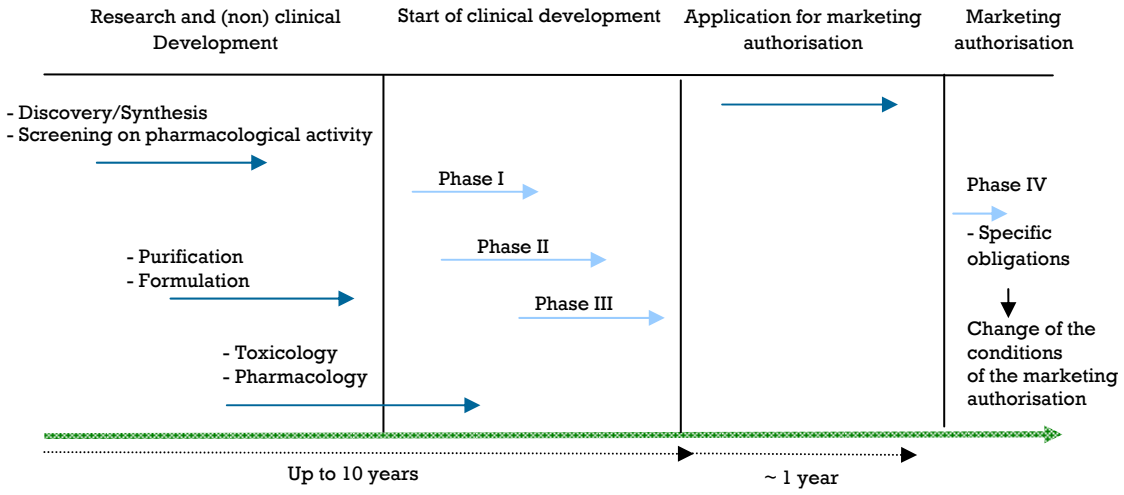
[25] The European Commission's Pharmaceuticals website: http://ec.europa.eu/enterprise/pharmaceuticals/advtherapies/index.htm
[26] http://www.emea.europa.eu/htms/human/mes/introduction.htm

4. Medicinal Product Development (Human)

The data requirements for an application for marketing authorisation for a human medicinal product are laid down in EU legislation, in particular Annex I of Directive 2001/83/EC (see Sections 1.2 and 1.3). Guidance is available in the scientific guidelines adopted at ICH and EU levels, and in the Notice to Applicants (NTA)[27] which includes guidance on the Common Technical Document (CTD) (see Section 6.6)

An overview of the pharmaceutical, non-clinical and clinical development of a medicinal product for human use is provided in Sections 4.1-4.3 below. For detailed information, SME companies should consult the EMEA website where all current scientific guidelines are published (see Section 3.2).

To ensure that the appropriate studies are performed and that there are no major objections regarding the study design at the time of the evaluation of the marketing authorisation application, SMEs are particularly encouraged to seek scientific advice from the EMEA (see Section 3.1).

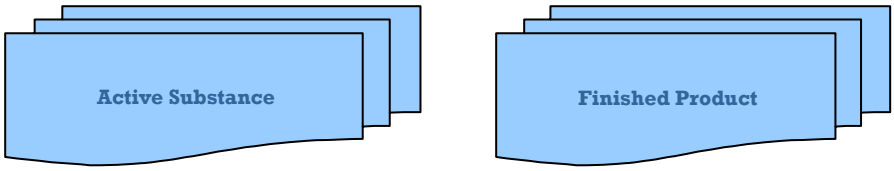


[27] The 'Notice to Applicants' is Volume 2 of 'The rules governing medicinal products in the European Union': http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/

© EMEA 2009

4.1 Quality

The pharmaceutical quality of a medicinal product consists of two main pillars:



The purpose of the pharmaceutical development is to develop a formulation that will be fit for its intended use, that is, to consistently deliver the active substance at the site of action at the required dose and that will be stable throughout its shelf-life.

4.1.1 Active substance (drug substance)

Active substance means a substance with physiological or pharmacological activity, which is responsible for the claimed clinical effect of the product, be it therapeutic, prophylactic or diagnostic. Depending on their source active substances can be classified as inorganic substances, herbal drugs and herbal preparations, 'chemical' (synthetic or semi-synthetic, or isolated from herbal sources or microorganisms) and biological active substances[28].

The amount of information to be generated during development depends on whether the active substance is a new substance, being used for the first time in a medicinal product,,or an existing active substance (either described in a pharmacopoeia, or not). However in all cases the active substance should be well characterised and manufactured by well-described and adequately controlled manufacturing methods (see Section 4.4.1, Good Manufacturing Practice).

For new active substances, applicants are encouraged to apply for an International Non-proprietary Name (INN) as early as possible in the clinical development. INNs are assigned by the WHO, to whom requests should be submitted[29].

When developing a medicinal product, the following key issues should be addressed with regard to active substances:

General information: Structural formula, including relative and absolute stereochemistry, molecular formula, and relative molecular mass. Examples of physicochemical and biological properties that might need to be examined include solubility, water content, particle size, crystal properties, biological activity, and permeability. The solid-state properties that might affect the *in vivo* performance are of particular importance. Additionally for proteinaceous biological active substances the schematic amino acid sequence indicating glycosylation sites or other post-translational modifications and biological activity should be available.

[28] Annex I of Regulation 1085/2003/EC
[29] For more information visit the WHO website: (http://www.who.int/medicines/services/inn/en/)

© EMEA 2009

Manufacture: The manufacturing process should be well-described and understood. All critical parameters should be identified and appropriately controlled. It should also be demonstrated that the process can reproducibly produce a substance with the desired quality characteristics. In addition the starting material, that is to say all materials from which the active substance is manufactured, should be evaluated and documented.

Biological active substances are often generated by cell substrates (microbial cells or cell lines derived from human or animal sources that possess the full potential for generation of the active substance). For cell substrates having a cell banking system, all procedures to generate the master cell bank and the working cell bank(s) should be documented. Characterisation and testing of banked cell substrates should be carried out to confirm their identity, purity, stability and suitability for manufacturing use. Particular attention should be given to potential contamination from adventitious agents (see Section 4.1.3).

When there is a change in the manufacturing process of a chemical or biological active substance, it should be ensured that it will not affect the product. For biological active substances in particular, consideration should be given to performing a comparability exercise. If the analytical data are not sufficiently reassuring, additional evidence from bridging non-clinical and clinical studies will be required.

Characterisation: Extensive characterisation is performed in the development phase and, where necessary, following significant process changes. Characterisation is necessary to allow relevant specifications to be established.

The potential for isomerism, identification of stereochemistry, and polymorphism should be evaluated. The purity of a substance is often judged by examining the impurities it contains. Therefore special emphasis should be given to characterising the impurities which arise from the method of manufacture and also those produced on storage, by degradation. Similarly, how impurities are generated should be described. When the level of impurities exceed certain thresholds found in the (V)ICH guidelines on Impurities [30], their toxicological significance becomes important from a safety point of view. Therefore these impurities have to be 'qualified' (usually with reference to formal toxicology studies) to demonstrate they are safe.

Control of Active Substance: Specifications are critical quality standards that are based on thorough characterisation and on the mechanistic understanding of how formulation and process factors can impact product performance. Specifications should reflect the characteristics an active substance should have to meets its intended purpose. Conformity with specifications should provide assurance that quality is maintained from the time of release to the end of the shelf-life/re-test period. The acceptance criteria should be established and justified based on data obtained during development, including manufacturing consistency studies, stability studies and lots used in non-clinical and/or clinical studies. The analytical procedures that will be used to test the critical-to-quality attributes should be adequately validated in accordance with (V)ICH guidelines.

[30] Scientific guidelines for human and veterinary medicinal products:
http://www.emea.europa.eu/htms/human/humanguidelines/background.htm
http://www.emea.europa.eu/htms/vet/vetguidelines/background.htm

© EMEA 2009

Stability: The applicant should study how the quality of the active substance varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. This will allow the definition of practical storage conditions and a 'window of use' called the shelf life/re-test period (during which the substance may be used without further testing).

Submission of information for active substances: There are three ways to present the information relating to the active substance in a marketing authorization application:

- *Full data* are presented in the dossier (in accordance with either the CTD or NTA structures).
- *Active Substance Master File* (ASMF): In order to protect the intellectual property of the active substance manufacturer, it is possible to submit information relating to the manufacturing process, controls and validation in a separate document (ASMF) submitted directly to the competent authorities by the manufacturer of the active substance. The concept of the ASMF applies only to ''well-defined active substances''. It therefore cannot be used for biological active substances, excipients, finished products, container materials, etc.
- *Certificate of Suitability (CEP):* The applicant may apply to the European Pharmacopoeia secretariat[31] with documentation requesting the evaluation of the Ph.Eur. monograph in relation to the manufacturing method actually used. If a CEP is issued, then no additional information needs to be submitted for those parts of the dossier covered by the CEP, except where relevant information on sterility, particle size, etc, is necessary.

4.1.2 Finished product (drug product)

The key issues that applicants should address during the development of the finished product are summarised below:

Formulation development: When developing a formulation it is important to identify attributes that are critical to the quality of the finished product, taking into consideration its intended usage and route of administration.

The potential effect of the physicochemical properties of the active substance (for example, water content, solubility, particle size distribution, polymorphic or solid state form) on the performance of the finished product should be evaluated. Other key issues to be investigated are the compatibility of the active substance with excipients, containers and closures. For combination products, the compatibility of active substances with each other should also be evaluated.

It is highly likely that during the product's development there will be changes in the formulation and manufacturing process. In all cases the differences between the clinical formulations used and the formulation intended to be marketed should be discussed and their equivalence demonstrated (using either *in vitro* or comparative *in vivo* studies, as appropriate).

If the formulation contains a novel excipient, that is, an excipient used for the first time in a medicinal product, or by a new route of administration, then full details of its manufacture, characterisation and control, with cross references to supporting safety data (non-clinical and/or clinical) should be provided. As there can be no confidential master file for excipients, applicants should provide information in the application for marketing authorisation.

---

[31] For more information visit the European Directorate for the Quality of Medicines (EDQM) website http://www.pheur.org/site/page_628.php

Microbiological attributes: All parameters relevant to the microbiological attributes of the dosage form should be evaluated. Examples include, the selection and effectiveness of preservative systems in products containing antimicrobial preservatives, and, for sterile products, the sterilisation process, the integrity of the container/closure system for prevention of microbial contamination. The compatibility of the drug product with reconstitution diluent(s) or dosage devices (e.g. precipitation of drug substance in solution, sorption on injection vessels, stability) should also be demonstrated.

Process development: It is important to consider the critical formulation attributes, together with the manufacturing process options, in order to address the selection of the manufacturing process and confirm the appropriateness of its components. In general, process development studies should provide the basis for process improvement, process validation and continuous process verification.

For manufacturing process changes for biological/biotechnological products, the same recommendations as mentioned above (for active substances) apply.

Manufacture - control of excipients and finished product and stability: As with active substances, the manufacturing process used for the finished product should be carefully designed so that it consistently produces product of the intended quality. All critical steps should be identified and controlled (for Quality by Design, see Section 4.1.3). Appropriate specifications should be set for the excipients and the finished product and validated methods should be used for their testing. The stability of the finished product should be demonstrated throughout its proposed shelf life, and in-use shelf life, under the proposed conditions.

4.1.3 Other Specific Issues

Adventitious agents: All materials of human or animal origin used in the manufacturing processes of either the active substance or the finished product, or coming into contact with the active substance or finished product during the manufacturing process should be identified. The risk with respect to potential contamination with adventitious agents of human or animal origin should be assessed.

- TSE agents: The current "Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products, EMEA/410/01[32]" should be applied. Suppliers of any substances with a TSE risk used in production or preparation of medicinal products can apply to the Ph. Eur. for a TSE certificate. Such certificates can then be used by marketing authorisation applicants (for more information see the EDQM website[33])
- Viral safety: The risk of introducing viruses into the product and the capacity of the manufacturing process to remove or inactivate viruses should also be evaluated.
- Other adventitious agents: Detailed information regarding other adventitious agents, such as bacteria, mycoplasma and fungi should be provided.

Quality by Design: The term Quality by Design is often used to describe an optional more systematic approach to pharmaceutical development, which may include, amongst others, the use of analytical, statistical and risk management tools in order to obtain an in-depth understanding of the product and the process. For more information see the Note for Guidance on Pharmaceutical Development[34], ICH Q8 and the EMEA website[35].

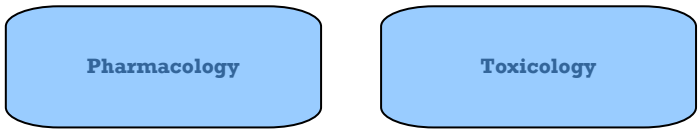
---

[32] http://www.emea.europa.eu/pdfs/human/bwp/TSE%20NFG%20410-rev2.pdf
[33] EDQM website: http://www.edqm.eu/site/News_amp_General_Information-164.html
[34] Note for Guidance on Pharmaceutical Development (EMEA/CHMP/167068/2004-ICH) is available on the EMEA website
[35] http://www.emea.europa.eu/Inspections/PAThome.html

© EMEA 2009

4.2 Non-clinical Development

The non-clinical development consists of two main parts:



The purpose of non-clinical development is to evaluate the pharmacodynamic and toxicity profile prior to initiating clinical studies, to predict potential safety problems and to investigate particular safety aspects as detailed below.

Some of the non-clinical studies need to be performed before administration of first dose to man while others can run in parallel to clinical trials (see Figure 1). The summary below outlines the important tests generally required, for comprehensive details please refer to the relevant scientific guidelines (Section 3.2). ICH M3[36] and CHMP Guidance on first-in-human clinical trials (EMEA/CHMP/SWP/28367/07)[37] provide guidance on the non-clinical safety studies required for the conduct of clinical trials.

4.2.1 Pharmacology

This part of the development addresses the pharmacodynamics of a new product in the non-clinical setting.

Pharmacodynamics

The pharmacodynamics includes investigation of the "primary" pharmacodynamics, which comprises the effects related to the proposed therapeutic indication. In addition, investigation of the "secondary" pharmacodynamics (effects other than those related to the proposed therapeutic indications) is required. Safety pharmacology addresses undesired pharmacodynamic effects on specific physiological systems, mainly central nervous, cardiovascular and respiratory systems in relation to exposure in the therapeutic range and above.

Finally it is necessary to investigate pharmacodynamic drug interactions with medicinal products that are likely to be administered for the same condition.

Pharmacokinetics

This part of the development comprises studies investigating absorption, excretion, tissue distribution, metabolism and pharmacokinetic drug interactions. The area under the matrix level concentration-time curve (AUC), C_{max} at the expected peak concentration and C (time) at certain time points after administration are the most commonly used parameters in assessing exposure in pharmacokinetics studies. Other

[36] Note for Guidance on Non-clinical safety studies for the Conduct of Human Clinical Trials for Pharmaceuticals (CPMP/ICH/286/95 – ICH M3): http://www.emea.europa.eu/pdfs/human/ich/028695endraft.pdf
[37] Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07): http://www.emea.europa.eu/pdfs/human/swp/2836707enfin.pdf

© EMEA 2009

parameters include urinary exposure, bioavailability, half-life, and fraction of unbound drug and volume of distribution.

4.2.2 Toxicology

The following studies should generally be performed during the development.

Single-dose and repeated dose toxicity: The primary goal is to characterise the toxicological profile of the medicinal product following repeated administration. This includes identification of target organs of toxicity, exposure response relationship and potential reversibility of toxic effects. Unless justified, experiments in two species are required one of which should be non-rodent and the duration depends upon the planned human use. For products for chronic use in humans, repeated dose toxicity studies of six months duration are requested. In addition to investigating toxicity, the kinetics should be investigated in the repeated-dose toxicity studies (toxicokinetics). The toxicokinetics provide a means of obtaining multiple dose pharmacokinetic data in the test species; the parameters assessed are the same as in pharmacokinetic studies.

Reproductive toxicity: The primary goal is to investigate the effects of the medicinal product on the following steps of reproduction:

- male and female fertility and early embryonic development (e.g. implantation) in one species, usually rats;
- embryofetal development (development of organs during pregnancy) in two species, one of which should be a non-rodent (usually rabbit);
- prenatal and postnatal development in one species, usually rats.

Genotoxicity: Genotoxicity tests can be defined as *in vitro* and *in vivo* tests designed to detect compounds which induce genetic damage in the DNA directly or indirectly by various mechanisms. The standard battery comprises tests for genotoxicity in bacteria (Ames test), as well as *in vitro* tests for genotoxicity in mammalian cells and test for chromosomal damage (micronucleus test usually in the mouse). Compounds which are genotoxic have the potential to induce cancer and/or heritable defects. Genotoxicity test are generally required for any product, with the exception of most biological products.

Carcinogenicity: The objectives of carcinogenicity studies are to identify tumorigenic potential in animals and to assess the relevant risk in humans. They are required for pharmaceuticals expected to be administered regularly over a period of at least 6 months and for pharmaceuticals used frequently in an intermittent manner in the treatment of chronic or recurrent conditions. For pharmaceuticals administered infrequently or for a short duration of exposure (e.g. anaesthetics and radiolabelled imaging agents) carcinogenicity studies are not needed unless there is cause for concern. For anticancer medicinal products carcinogenicity studies are normally also not required.

The carcinogenicity battery consists of two long-term (1.5-2-years) studies in the rat and mouse or one long-term study in the rat and one short-term study (6-months) in a transgene model.

Immunotoxicity: In the context of medicinal product development, it is defined as unintended immunosuppression or enhancement. All new human pharmaceuticals should be evaluated for the potential to produce immunotoxicity. Methods include evaluating parameters of the immune system in the standard repeated dose toxicity studies mentioned above and additional immunotoxicity studies conducted, as appropriate, if there is cause for concern. In case additional specific immunotoxicity studies are required, a generally accepted study design in rodents is a 28-day study with

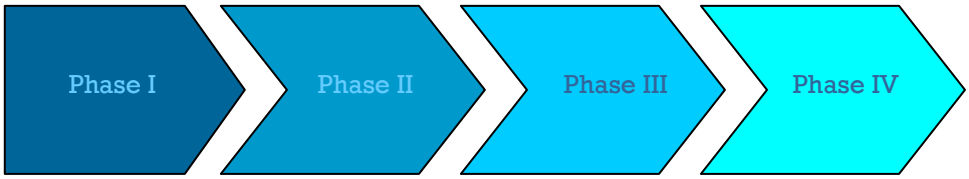
consecutive daily dosing. Endpoints can include T-cell dependent antibody response and immunophenotyping of leucocyte populations.

Local tolerance: The purpose of these studies is to investigate whether pharmaceuticals are tolerated at sites of the body that may come into contact with the product as a result of its administration in clinical use. Usually one species is required for each type of test (e.g. ocular tolerance and skin toxicity in the rabbit) and the route of administration is guided by the envisaged clinical use. The local tolerance can be specifically evaluated as part of the repeated dose toxicity study or as a specific study (usually single or repeated administration over a number of days).

Environmental risk assessment: The purpose of these tests, which are required for all new medicinal products, is to investigate the potential environmental risk of the new medicinal product under development. The first part of the investigation assesses the exposure of the environment to the active substance. Based on an action limit the assessment of environmental risk may be terminated at this stage. Above certain limits, the fate of the substance in and the effects on the environment should be investigated in a second phase of investigation. The extent of the required tests depends on the exposure and fate in the environment, e.g. a long-term toxicity study in fish, daphnia and algae may be required to determine the predicted no-effect concentration.

4.3 Clinical development

Clinical development is often described as consisting of four temporal phases:



The purpose of clinical development is to establish a dose-response relationship, demonstrate the efficacy and establish the safety profile of a medicinal product in a therapeutic indication in order to provide an adequate basis for assessing the benefit/risk relationship to support licensing.

The phase concept is a description of the objectives which are summarised below, not a set of requirements. It is also important to realise that the temporal phases do not imply a fixed order of studies since for some medicinal products in a development plan the typical sequence will not be appropriate or necessary. Detailed information is available in the ICH E8 'Note for guidance on general considerations for clinical trials' (CPMP/ICH/291/95)[38]. For comprehensive details please refer to the relevant scientific guidelines (Section 3.2).

4.3.1 Phase I – Human Pharmacology studies

The initial administration of a new product into humans takes place in phase I. Studies in this phase of development do not aim to assess efficacy and may be conducted in healthy volunteer subjects or certain types of patients, e.g. patients with mild hypertension. Due to ethical reasons medicinal products with significant potential toxicity, e.g. cytotoxic compounds used in cancer treatment, are usually studied in patients already in this phase.

The objectives of these studies typically involve one or a combination of the following:

[38] Available on the EMEA website: http://www.emea.europa.eu/pdfs/human/ich/029195en.pdf

© EMEA 2009

Using both single and multiple administration of increasing doses, initial safety and tolerability is assessed, which helps guide the dose for future therapeutic trials. Preliminary characterisation of absorption, distribution, metabolism, and excretion (pharmacokinetics) is another goal of phase I studies. For many orally administered medicinal products, especially modified release products, the study of food effects on bioavailability is important. Moreover, depending on the product and the endpoint studied, pharmacodynamic studies and studies relating blood levels of the product to response (PK/PD studies) may be conducted in healthy volunteer subjects or in patients. Pharmacodynamic endpoints may include biochemical or physiological parameters, receptor occupancy etc. Although clinical activity is normally not the goal of this first phase, in some cases data may be collected as a secondary objective; for example, when assessing the pharmacokinetics of a sleeping pill it is possible to obtain some results on potential activity (sleep-inducing effect).

4.3.2 Phase II – Therapeutic exploratory studies

The goal of this phase is to explore therapeutic activity in patients. Studies in phase II are typically conducted in a group of patients who are selected by relatively narrow criteria, leading to a relatively homogeneous population. An important goal for this phase is to determine the dose(s) and regimen for phase III trials. Early studies in this phase often utilise dose escalation designs (see Note for guidance ICH E 4)[39] to give an early estimate of dose response, whereby an initial low dose is increased until optimal response or until occurrence of adverse events. The dose response relationship for the indication in question can be confirmed in later parallel dose-response design studies. In this phase, therapeutic activity can be explored using endpoints, which can be evaluated in a shorter time period than the actual therapeutic goal. For example, shrinking of the tumour mass in a particular cancer could be a suitable endpoint to assess activity in phase II, but would normally not be sufficient to demonstrate efficacy in phase III, where "hard" clinical endpoints like survival of the patient would be more relevant. When the results of this phase become available, it is decided if it is justified to proceed to the extensive phase III development.

4.3.3 Phase III – Therapeutic confirmatory

The goal of phase III trials is to demonstrate therapeutic benefit and to confirm the preliminary evidence accumulated in phase II. These studies are intended to provide an adequate basis for marketing approval. Therefore a sufficiently high number of patients must be enrolled (usually several hundred to several thousand) and exposed to the investigational medicinal product for a duration which will provide adequate efficacy and safety data for the envisaged clinical use. Generally for medicines being developed for chronic use studies of at least 6 months duration are required. The studies must generally be controlled, i.e. compare the product under development to placebo (a pharmaceutical preparation containing no active agent, made to look just like the test compound) and/or to active treatment depending on the condition and the product under investigation. In addition the studies must generally be double-blind, i.e. neither the treating physician nor the patient know the treatment administered (test drug, placebo, active comparator). Usually two phase III trials would be required for approval but under specific circumstances one well-conducted large trial may be sufficient. In addition to clinical efficacy, demonstration of safety is the second important goal of this phase. The requirements for investigating the adverse events profile are described in the ICH E 1: 'Note for guidance on population exposure: the extent of population exposure to assess

[39] ICH E4 'Note for guidance on dose response information to support drug registration' (CPMP/ICH/378/95) is available on the EMEA website. http://www.emea.europa.eu/pdfs/human/ich/037895en.pdf

clinical safety' (CPMP/ICH/375/95)[40]. Generally, 300-600 patients treated for six months and 100 patients exposed for a minimum of one-year are considered to constitute an acceptable safety database. However, clinical trials before marketing authorisation have limitations to detect rare adverse events. An event occurring in less than 1: 1,000 patients will normally not be detected in the pre-marketing phase.

4.3.4 Phase IV – Therapeutic use

These are studies related to the approved therapeutic indication which are conducted postmarketing. Their goal is to gather additional information about the medicinal products benefits, risks and optimal use in the broad population. Commonly conducted studies include additional drug-drug interaction, dose-response or safety studies and studies designed to support use under the approved indication, e.g. mortality/morbidity studies, epidemiological studies.

4.3.5 Clinical trials – Notice to applicants

A compilation of legislative and guidance documents in the field of clinical trials, referred to as the 'Notice to Applicants Volume 10– Clinical Trials'[41] has been published by the European Commission and includes guidance on:

- application for starting a clinical trial, to be submitted to the competent authorities of the Member States and the Ethics Committees;
- guidance on the European clinical trials database (EudraCT Database)
- safety monitoring and reporting of adverse reactions arising during clinical trials;
- requirements for manufacturing and import authorisation of Investigational Medicinal Products (IMP);
- qualification of inspectors and inspection procedures;
- the modalities for non-commercial trials;
- recommendation for the trial master file and archiving;

EudraCT is a database of all clinical trials initiated in the Community from 1 May 2004 onwards. It has been established in accordance with Article 11 of the clinical trial Directive 2001/20/EC which states that this database is only accessible to Member States, the agency and the Commission. However Article 41 of the paediatric regulation 1901/2006/EC states that by way of derogation from the provisions of Article 11 of Directive 2001/20/EC, EMEA shall make public part of the information on paediatric clinical trials entered in the EudraCT.
The EudraCT website[42] is the sponsor interface which gives the sponsor access to the EudraCT application in order to:

- get a EudraCT number.
- submit a clinical trial application form to the competent authorities and Ethics Committees.

A clinical trial application consists of administrative information and the necessary demonstration of quality, safety and efficacy of the investigational medicinal product (IMP). With regards to the quality of the IMP, it is anticipated that in the early development stages information on the analytical methods, their validation, the setting of specifications and the stability might be incomplete. For this reason, for human medicinal products, different requirements are set for IMPs to be used in phase I, II and III trials. For further information the 'CHMP Guideline on the chemical and pharmaceutical quality

[40] Available on the EMEA website: http://www.emea.europa.eu/pdfs/human/ich/037595en.pdf
[41] Volume 10 of the rules governing medicinal products in the European Union http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/index.htm
[42] EudraCT website: http://eudract.emea.europa.eu/

© EMEA 2009

documentation concerning investigational medicinal products in clinical trials' (CHMP/QWP/185401/04)[43] should be consulted.

SME companies should be aware that if the final formulation differs from that of the IMP used in earlier clinical trials, the relevance of the earlier material compared to the product tested in later phases should be described. Special consideration should be given to changes in quality parameters with potential clinical relevance, e.g., *in vitro* dissolution rate.

4.4 GMP/GCP/GLP

4.4.1 Good Manufacturing Practice (GMP)

Good Manufacturing Practice (GMP) is defined as that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use. The principles and guidelines for GMP are stated in two Directives: Directive 2003/94/EC [44] for medicinal products and investigational medicinal products for human use and Directive 91/412/EEC[45] concerning veterinary medicinal products. Compliance with these principles and guidelines is mandatory within the European Economic Area. Interpretation of these requirements is provided in 'EU guidelines to Good Manufacturing Practice - Medicinal products for human and veterinary use'[46] published by the European Commission. This guide to GMP consists of detailed guidelines (part I and part II) which are supplemented by a series of annexes specific for certain types of product or topics.

Manufacturing authorisation holders are obliged to comply with GMP requirements for medicinal products and to use as starting materials only active substances manufactured in accordance with the guidelines on GMP for starting materials. It is the responsibility of the batch release/manufacturing site for the finished product to ensure and declare that their suppliers of active substances comply with GMP requirements for active substances.

4.4.2 Good Clinical Practice (GCP)

Good Clinical Practice (GCP) concerning human medicinal products is an international ethical and scientific quality standard for designing, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and wellbeing of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible. Requirements for the conduct of clinical trials in Europe including GCP and GMP and inspections of these, have been implemented in the Clinical Trial Directive (Directive 2001/20/EC)[47] and GCP Directive (2005/28/EC)[48]. This regulatory framework is published in the 'Notice to Applicants – Clinical Trials'[49]. Clinical trials included in any marketing authorisation application in the EU are legally required to be conducted in accordance with GCP.

---

[43] Included in Volume 10 of the rules governing medicinal products in the European Union and also available on the EMEA website.
[44] *Official Journal L 262, 14/10/2003 p. 22 - 26*
[45] *Official Journal L 228, 17/8/1991 p. 70 - 73*
[46] Volume 4 of the rules governing medicinal products in the European Union http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/index.htm
[47] *Official Journal L 121, 1/5/2001 p. 34 – 44*
[48] *Official Journal L 91, 9/4/2005, p.13-19*
[49] Volume 10 of the rules governing medicinal products in the European Union http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/index.htm

© EMEA 2009

For clinical trials of veterinary products, Europe has adopted the Veterinary ICH GL9 'Guideline on good clinical practices' CVMP/VICH/595/98[50], which provides guidance on the design and conduct of all clinical studies of veterinary products in the target species. It is directed at all individuals and organisations involved in the design, conduct, monitoring, recording, auditing, analysis and reporting of clinical studies in target species and is intended to ensure that such studies are conducted and documented in accordance with the principles of GCP. The Annex to Directive 2001/82/EC[51] as amended, sets out conditions for the conduct of clinical trials included in applications for marketing authorisation.

4.4.3 Good Laboratory Practice (GLP)

Good Laboratory Practice (GLP) defines a set of rules and criteria for a quality system concerned with the organisational process and the conditions under which non-clinical studies are planned, performed, monitored, recorded, reported and archived. Detailed information about GLP can be found on the linked websites of the Organisation for Economic Co-operation and Development (OECD)[52] and the European Commission[53] (see Directive 2004/9/EC[54] and 2004/10/EC[55]). For human products, Annex I to Directive 2001/83/EC[56] as amended indicates that safety tests reported in marketing authorisation applications should be performed in compliance with the principles of GLP. For veterinary products, in accordance with Annex I to Directive 2001/82/EC[57] as amended the same principles apply, as well as for tests carried out for the establishment of maximum residue limits of veterinary medicinal products in foodstuffs of animal origin.

4.4.4 Inspections

GMP, GCP and GLP Inspections may be requested in connection with an application for a marketing authorization at national or a community level. The sites to be inspected (manufacturing and quality control sites and/or non-clinical study sites and/or clinical trials sites) should be "inspection ready" at the time of submission of the application and throughout the assessment.

The EMEA is responsible for the co-ordination of pre-authorisation GMP, GCP, GLP and pharmacovigilance inspections in connection with the granting of a marketing authorisation by the Community. All information concerning centralised inspections activities can be found on the Inspection section of the external EMEA web page.[58] Additional information is available in the EMEA pre-submission guidance (see Section 6.1).

4.5 Measures for orphan medicines and paediatrics

4.5.1 Orphan medicinal products

Orphan designation:
'Orphan' medicinal products are those intended to diagnose, prevent or treat life-threatening or very serious conditions that are rare and affect not more than 5 in 10,000 persons in the European Union.

---

[50] VICH GL9 'Guideline on good clinical practices' (CVMP/VICH/595/98) is available on the EMEA website. http://www.emea.europa.eu/pdfs/vet/vich/059598en.pdf
[51] *Official Journal L 311, 28/11/2001 p. 1 - 66*
[52] OECD website : http://www.oecd.org/env/glp
[53] http://ec.europa.eu/enterprise/chemicals/legislation/glp/index_en.htm
[54] *Official Journal L 50, 11/2/2004 p. 28 – 43*
[55] *Official Journal L 50, 20/2/2004 p. 44 – 59*
[56] *Official Journal L 311, 28/11/2001 p. 67 – 12*
[57] *Official Journal L 311, 28/11/2001 p. 1 - 66*
[58] http://www.emea.europa.eu/Inspections/index.html

© EMEA 2009

Incentives:
EU incentives available from the EMEA for sponsors [59] /pharmaceutical industry developing orphan medicinal products include:

- a 10 year period of market exclusivity after the grant of a marketing authorisation;
- protocol assistance (scientific advice, see Section 3.1.1);
- fee reductions for certain centralised activities;
- direct access to the EMEA centralised procedure for the application for marketing authorisation.

Detailed information on incentives is available in the 'Inventory of Community and Member States' incentive measures to aid the research, marketing, development and availability of orphan medicinal products. Revision 2005'[60] published by the European Commission.

To be eligible for orphan incentives medicinal products should be designated through the Community procedure for orphan designation. Orphan designation may be obtained at any stage of development provided proper scientific justification of the intended use is submitted. The EMEA, through its Committee for Orphan Medicinal Products (COMP) is responsible for reviewing designation applications and issuing an opinion, which is transformed into a decision by the European Commission.

Guidance on the format and content of applications for designation as orphan medicinal products (ENTR/6283/00) [61] and an application form in Annex to Guideline are available from the EMEA. The designation procedure attracts no fees. Full details on how to apply (including guidance on calculation and reporting of the prevalence and the elements to support medical plausibility and the assumption of significant benefit) are available on the EMEA website[62].

To facilitate the application process, for those sponsors which also plan to request orphan designation from the United States Food and Drug Administration (FDA), a common application form for use is both regions is now available on the EMEA web-site.

The EMEA offers assistance to sponsors on preparation of orphan designation applications through free pre-submission meetings. for more information contact: orphandrugs@emea.europa.eu

The agency also provides free advice on the development of orphan medicinal products following designation (protocol assistance, see Section 3.1.1).

Orphan marketing authorisation:
Prior to the grant of a marketing authorisation the COMP will review the criteria on which the orphan designation has been based. Accordingly, at the time of submission of the application for marketing authorisation, the applicant is asked to submit a report to the Scientific Advice and Orphan Drugs sector at the EMEA demonstrating that the orphan criteria are still met.

---

[59] 'Sponsor' means any legal or natural person, established in the Community, seeking to obtain or having obtained the designation of a medicinal product as an orphan medicinal product.
[60] http://ec.europa.eu/enterprise/pharmaceuticals/orphanmp/index.htm
[61] Guideline on the Format and Content of Applications for designation as Orphan Medicinal Products (ENTR/6283/00) http://www.emea.europa.eu/pdfs/human/comp/628300en.pdf
[62] http://www.emea.europa.eu/htms/human/orphans/intro.htm

In accordance with Article 8 of Regulation (EC) No 141/2000[63], once a designated orphan medicinal product is authorised in all EU Member States, it is granted a ten year period of market exclusivity. This market exclusivity protects the originator's medicinal product in the authorised 'orphan' therapeutic indication. As such, 'similar' medicinal products will not be granted a marketing authorisation for the same therapeutic indication unless the originator gives consent, is unable to supply sufficient quantities of the medicinal product, or the second applicant demonstrates that although similar, the medicinal product is clinically superior to the originator.

The definitions of 'similar' medicinal product and 'clinically superior', in this context, are laid down in Article 3 of Commission Regulation (EC) No 847/2000[64].

It is important for SMEs to note when preparing an application for marketing authorisation, that where a designated orphan medicinal product has been authorised for the condition which covers the proposed therapeutic indication being applied for, and a period of market exclusivity is in force, the possible 'similarity' with the authorised orphan medicinal product must be addressed in the application for marketing authorisation. If applicable, the applicant must then argue clinical superiority or justify that one of the derogations noted above applies.

The overall judgment of similarity includes an evaluation of the indication, the mechanism of action and the molecular structure.

4.5.2 Paediatric Requirements

New legislation governing the development and authorisation of medicines for use in children was introduced in the European Union in January 2007.

The overall aim of the new legislation — Regulation (EC) No 1901/2006 as amended (the 'Paediatric Regulation') — is to improve the health of the children in the EU by increasing the research, development and authorisation of medicines for use in children. To this end, a system of obligations, incentives and rewards has been put in place as outlined below:

System of obligations, incentives and rewards:

For unauthorised medicinal products

- Since 26 July 2008, there will be an obligation to submit the results of studies conducted according to a paediatric investigation plan (PIP)[65] in order to have a valid application for a new marketing authorisation throughout the EU. A waiver may be requested for medicines that are unlikely to benefit children. In some cases, studies may be deferred until after the medicine has been authorised for use in adults.
- The reward for conducting the paediatric development in compliance with a paediatric investigation plan is a six-month extension of the supplementary protection certificate[66], provided that the results are included in the product information and that authorisation is obtained in all EU Member States.

[63] *Official Journal L 18, 22/1/2000 p. 1 – 5*
[64] *Official Journal L 103, 27/4/2000 p. 5-8*
[65] The PIP is a research and development programme aimed at ensuring that the necessary data are generated to determine the conditions in which a medicinal product may be authorised for the paediatric population.
[66] With reference to Council Regulation (EEC) No 17687/92 of 18 June 1992.

© EMEA 2009

For orphan medicinal products

- The obligations for unauthorised medicinal products outlined above also applies. The reward is two years of market exclusivity in addition to the existing 10-year exclusivity awarded under the EU Orphan Regulation, provided that the results are included in the product information and that authorisation is obtained in all EU Member States.

For authorised patented medicinal products

- As of 26 January 2009, there will be an obligation to submit the results of studies conducted in accordance with an agreed paediatric investigation plan when seeking a variation or extension of the marketing authorisation for a new indication, new route of administration or new pharmaceutical form. As with new medicines, waivers or deferrals may also be granted, and the reward is a six-month extension of the supplementary protection certificate.

For off-patent medicinal products

- Off-patent medicines developed solely for paediatric use and with an appropriate formulation can benefit from a new type of marketing authorisation — the paediatric-use marketing authorisation (PUMA) — which benefits from 10 years of data protection. The obligations referred to above concerning the PIP also apply.

Other key measures in the paediatric regulation include:

- Community funding for research on off-patent medicines delivered through the Community Framework Programme;
- measures to increase the robustness of pharmacovigilance (safety monitoring) for medicines;
- a requirement for industry to submit to the authorities study reports they already hold on use of their medicines in children, to maximise the utility of existing data and knowledge;
- an EU inventory of the therapeutic needs of children to focus research, development and authorisation of medicines;
- an EMEA-based EU network of investigators and trial centres to conduct research and development on medicines for children;
- public access to some information on protocols and results of paediatric clinical trials in the European Database of Clinical Trials.

It is important for SMEs to be aware that there is a requirement to agree the paediatric investigation plan early in development, by the time human pharmaco-kinetic studies are completed in adults. The EMEA, through its Paediatric Committee (PDCO) is responsible for assessing the content of paediatric investigation plans, waivers and deferrals and formulating an opinion, which is subsequently transformed into a decision.

Guidance on the format and content of applications for agreement or modification of a paediatric investigation plan, requests for waivers or deferrals, the operation of the compliance check and on criteria for assessing significant studies[67] is available from the EMEA. There is no fee associated with these applications. Full details on how to apply are available on the EMEA website[68].

The agency also provides free advice on the development of medicinal products for paediatric indications (see Section 3.1).

---

[67] Commission Guideline on the Format and Content of Applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies
http://ec.europa.eu/enterprise/pharmaceuticals/paediatrics/docs/draft_guideline_pip_2007-02.pdf

[68] http://www.emea.europa.eu/htms/human/paediatrics/introduction.htm

© EMEA 2009

Once the PDCO has agreed the PIP, the applicant company will need to comply with the plan. A compliance check will be necessary before any application for marketing authorisation (even for an adult indication) can be considered valid. To avoid delays in the validation process, applicants should request a compliance check at least 3 months in advance of submission.

SMEs are advised to familiarise themselves with the requirements by visiting the EMEA and Commission[69] websites. Questions relating specifically to the authorisation of paediatric medicines may be submitted to: paediatrics@emea.europa.eu

[69] http://ec.europa.eu/enterprise/pharmaceuticals/paediatrics/index.htm

© EMEA 2009

5. Medicinal Product Development (Veterinary)

The data requirements for an application for marketing authorisation for a veterinary medicinal product are laid down in EU legislation, in particular in Title II of Annex I of Directive 2001/82/EC as amended. Further guidance is available in the scientific guidelines adopted at VICH and EU level as well as in the Notice to Applicants[70]. In addition, many immunological veterinary medicinal products (IVMPs) are subject to the requirements of European Pharmacopoeia monographs.

Foodstuffs obtained from animals treated with veterinary medicinal products must not contain residues which might constitute a health hazard to the consumer. Therefore, no marketing authorisation for any veterinary medicinal product intended for food-producing animals can be granted in the European Union unless Maximum Residue Limits (MRLs) have been established for any pharmacologically active substance contained in the product. The establishment of MRLs is a Community procedure regulated by Council Regulation (EEC) No 2377/90, as amended[71]. The requirement for MRLs applies to the active principle(s) but also excipients or adjuvants, if they are pharmacologically active.

An overview of the studies required to establish the safety and efficacy of a medicinal product for veterinary use as well as MRLs is provided in Sections 5.1-5.4. For detailed information, SME companies should consult the EMEA website where all current scientific guidelines are published (see Section 3.2).

To ensure that the appropriate studies are performed and that there are no major objections regarding the study design at the time of the evaluation of the marketing authorisation application, SMEs are particularly encouraged to seek scientific advice from the EMEA (see Section 3.1).

5.1 Maximum Residue Limits (MRL)

In order to establish or modify MRLs for residues of veterinary medicinal products in foodstuffs of animal origin, an application should be submitted to the EMEA for evaluation by the CVMP. Procedural and administrative information e.g. dossier contents are explained in Volume 8 of the Notice to Applicants[72] and EMEA procedural guidance[73].

Safety and residue studies have to be conducted and submitted with an MRL application. These studies are intended to demonstrate that no harmful residues result in foodstuffs of animal origin from the normal conditions of use of the substance under consideration. Details on the studies to be conducted can be found on the EMEA website[74].

---

[70] (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-6/b/vol6b_04_2004_final.pdf
[71] http://ec.europa.eu/enterprise/pharmaceuticals/mrl/index.htm.
[72] http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-8/pdf/vol8_10-2005_.pdf
[73] EMEA SOP for submission and evaluation procedure for an application for the establishment of Maximum Residue Limits (MRLs): http://www.emea.europa.eu/pdfs/vet/sop/SOP081999.pdf

[74] Scientific guidelines for veterinary medicinal products:
http://www.emea.europa.eu/htms/vet/vetguidelines/background.htm

© EMEA 2009

Safety studies should include pharmacological, toxicological and other relevant studies such as studies on potential microbiological activity. The toxicological studies include repeat-dose toxicity, reproduction and developmental toxicity, genotoxicity and carcinogenicity testing, and testing of other effects, e.g. delayed neurotoxicity, where appropriate due to the type of substance.

The safety studies are required to establish the Acceptable Daily Intake (ADI). The ADI is an estimate of the substance and/or its residues, expressed in terms of □g or mg per kg body weight that can be ingested daily over a lifetime without any appreciable health risk to exposed individuals.

Residue studies, including pharmacokinetics tests, are required to determine the nature and actual level of residues and their elimination in the target animal and in particular edible tissues (muscle, fat or fat and skin, liver and kidney) and other food products of animal origin (milk, eggs or honey). Therefore, investigations of the elimination of residues from edible tissues and other food products of animal origin should be conducted. In order to allow the validation of the residue depletion studies and for the purpose of residue control validated analytical methods for identifying and measuring the residues in the tissues and food products should be developed.

On the basis of the safety and residue studies MRLs are established for the animal species for which the veterinary medicinal product is intended to be used (e.g. cattle). Where extension of existing MRLs to other animal species (e.g. extension to pigs) or specific food commodities (e.g. milk, eggs) is considered, only residue studies with regard to the relevant target species should be performed, because the ADI is the same regardless of the indications.

Modifications of the MRL can be requested, if new safety studies allow the modification of the ADI, or if new residue studies allow amendment of the MRLs.

At the end of the evaluation process the CVMP adopts an opinion, which is then submitted to the European Commission for adoption by the Standing Committee. Depending on the conclusions a pharmacologically-active substance may be inserted into one of the four annexes of Regulation 2377/90, three of which (Annex I, II and III) allow the use of the substance in food-producing animals. Further information on each of these Annexes can be found in the aforementioned Regulation or on the EMEA web pages on MRLs[75].

5.2 Quality

A common quality section, covering both medicinal products for human use and veterinary use, has been provided in this guide for ease of reference (see Section 4.1).

5.3 Safety

The safety of a product has to be demonstrated through "safety" studies, and for products intended for food-producing species also with "residue" studies. This part of development should address safety for the target animal (companion animals or food producing species), consumer safety, user safety and the environmental impact of the product.

Safety studies investigate the active substance(s) and excipients, if relevant. The research should focus both on the pharmacology (pharmacodynamics and pharmacokinetics) and toxicology.

---

[75] http://www.emea.europa.eu/index/indexv1.htm

The pharmacodynamic studies should take into account tests in experimental and target animals. The pharmacokinetic studies should investigate the absorption of active substance, its distribution, metabolism and excretion in animals.

Toxicology studies should assess single and repeated dose toxicity, tolerance in the target species, reproduction and developmental toxicity, genotoxicity and carcinogenicity. Tests on other effects such as immunotoxicity, dermal or eye irritation, neurotoxicity and antimicrobial properties might also be needed depending on the veterinary medicinal product. For products for food-producing animals many of the safety studies required for marketing authorisation will have been provided in the preceding MRL application.

An assessment of the user safety should be conducted, evaluating the risks for the persons that may be exposed to the product (pet owners, veterinarians, farmers, etc.) based on the safety studies conducted and considering the potential exposure.

An environmental risk assessment is required for all applications. The environmental risk assessment is conducted in two phases. In phase I an exposure driven screening is conducted to determine if the product leads to an extensive exposure of the environment. In most cases only data already available in the dossier are required. If, based on the conclusions of the phase I assessment, an in depth environmental risk assessment become necessary, specific investigations on the effects and fate in environment e.g. studies on effects on aquatic organisms and biodegradation, will be required (Phase II assessment).

Residue studies to establish a withdrawal periods should be carried out if the product is intended for use in food producing animals. These studies should include research on pharmacokinetics in the target species following administration by the intended route and take into account the edible tissues muscle, fat or fat and skin, liver and kidney, as well as milk, eggs or honey, as appropriate.

Additionally, the validated analytical method for the determination of residues suitable for use in the control of the established MRLs should be provided.

5.4 Efficacy

The efficacy of a product can be demonstrated with ''pre-clinical'' and ''clinical'' studies.

Preclinical studies should investigate the pharmacology, dose selection, tolerance in the target animal species and resistance development, if relevant. Usually these studies are undertaken in healthy animals, although some studies might also involve diseased animals.

Pharmacology studies should investigate the pharmacodynamics and pharmacokinetics (absorption, distribution, metabolism, excretion) relevant for the application i.e. for the proposed indication, dosage, route of administration and target species.

The pre-clinical studies should address the dose selection; this is usually done with dose determination (titration) studies. In the absence of such studies, e.g. for certain product classes or indications where such studies cannot be performed or would not provide adequate data, a justification for the proposed dose should be provided including references to other appropriate studies (e.g. dose confirmation/field studies).

Tolerance in the target species should usually be demonstrated by target animal tolerance studies using multiples of the recommended daily dose over an extended time

period. In addition and/or in cases where such classical studies cannot be conducted (e.g. for ethical reasons), this should be justified and other appropriate studies such as field or dose determination studies should be provided.

For antibiotic or anthelmintic products, the possibility of resistance development should be investigated in view of the potential impact on the efficacy of the product.

Clinical studies are performed in diseased animals, under laboratory and, ideally, under field conditions. These studies should provide a clear picture of the therapeutic efficacy and safety of the product, in comparison with other product(s) authorised for the same indication (positive control) or untreated animals (negative control). Field trials should include sufficient animal numbers and should usually be conducted in Europe with the final product formulation using the proposed dose, route and duration of administration. They should take into account different climatic/animal husbandry systems, especially for products such as anti-infectives and anthelmintics.

5.5 Immunologicals

Due to the widespread use of bovine serum in many IVMPs, specific measures concerning the prevention of the transmission of animal spongiform encephalopathies may be required (see Section 4.1.3).

If the IVMP contains or consists of genetically modified organisms (GMOs), as defined by Directive 2001/18/EC, the requirements of Article 31 (2) of Regulation EC 726/2004 on the authorisation of veterinary medicinal products which contain or consist of GMOs should be fulfilled.

Various tests and/or field studies should be conducted to show the potential risks from the product under the proposed conditions of use including target animal safety. For live vaccines, the assessment should focus on the potential shedding by vaccinated animals, the risk to unvaccinated animals or any other species and the potential of the strain used to revert to virulence.

Various tests and/or field trials should be conducted to confirm efficacy of the product in relation to all claims made for the product with regard to the properties, effects and use.

5.6 GMP/GLP/GCP

A common GMP/GLP/GCP section, covering both medicinal products for human use and veterinary use, is provided in this guide for ease of reference (see Section 4.4).

6. Application for Centralised Marketing Authorisation

6.1 Access to the centralised procedure

The centralised procedure is mandatory for certain types of human medicinal products such as those developed by certain biotechnological processes, designated orphans, and those containing new active substances for the treatment of acquired immune deficiency syndrome, cancer, neurodegenerative disorders, diabetes, auto-immune diseases, other immune dysfunctions and viral diseases..

The centralised procedure may also be used on a voluntary basis for other innovative medicinal products, or products for which the granting of a Community marketing authorisation would be in the interests of patients at EU level,. Further guidance on the mandatory (EMEA/CHMP/121944/2007) [76] and optional scope [77] of the centralised procedure, is given on the EMEA website and Commission website respectively.

The centralised procedure is mandatory for veterinary products developed by certain biotechnological processes and for medicinal products intended primarily for use as performance enhancers. The centralised procedure may be used on a voluntary basis for other innovative products, veterinary products for which the granting of a Community marketing authorisation would be in the interests of animal health at EU level, and immunological products for the treatment of animal diseases subject to EU prophylactic measures,.

Applicants wishing to use the centralised procedure, should notify the EMEA of their intent to submit an application as early as possible, and at least seven months in advance of the planned submission. The letter of intent should justify why the product qualifies for evaluation via the centralised procedure. Following discussion at CHMP or CVMP, the EMEA will inform the applicant whether the product falls within the mandatory or optional scope of the centralised procedure or not. Further guidance on how to request access to the centralised procedure, is given in the EMEA pre-submission guidance[78] on the EMEA website.

6.2 Selection of Rapporteur/Co-Rapporteur

For any scientific evaluation in the centralised procedure, a 'Rapporteur', and if relevant a 'Co-Rapporteur', will be appointed from the members of the CHMP/CVMP or the alternates. The role of the (Co-)Rapporteur is to perform the scientific evaluation and to prepare an assessment report to the CHMP/CVMP according to an agreed timetable.

The appointment of the Rapporteur/Co-Rapporteur is made on the basis of objective criteria, which will ensure the provision of objective scientific opinions and will allow the use of the best and available expertise in the EEA in the relevant scientific area.

The appointment process for Rapporteur/Co-Rapporteur is usually initiated at the CHMP/CVMP meeting following the receipt of the letter of intent to submit. In general, such intention letter including a request for Rapporteur/Co-Rapporteur appointment should optimally be provided **seven months** before the intended submission date of the application for a Marketing Authorisation. Further guidance on the appointment of

---

[76] 'Scientific aspects and working definitions for the mandatory scope of the centralised procedure (EMEA/CHMP/121944/2007) http://www.emea.europa.eu/pdfs/human/regaffair/12194407en.pdf

[77] The draft 'guideline concerning the optional scope of the centralised procedure in accordance with Article 3(2)(b) of Regulation (EC) No 726/2004' was released for consultation in December 2005 and once final will be included in volume 2C of the rules governing medicinal products in the European Union. http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2005/12-05/optional_scope_publ_21_12_05.pdf

[78] http://www.emea.europa.eu/– Human Medicines - Application Procedures - 'Pre-Submission Guidance' and http://www.emea.europa.eu/–Veterinary Medicines - Application Procedures - 'Pre-Submission Guidance

© EMEA 2009

Rapporteur and Co-Rapporteur for human medicinal products (EMEA/124066/05)[79] and veterinary medicinal products (EMEA/CVMP/928/02)[80], is given on the EMEA website.

If the intended application is deemed to be admissible, the EMEA will inform the applicant of the names of the Rapporteur and the Co-Rapporteur appointed by the CHMP/CVMP and will provide information on the applicable fees and dossier requirements of the CHMP/CVMP members.

The Rapporteur and Co-Rapporteur will select the experts of their assessment teams from the list of European Experts[81] accessible through the EMEA website.

6.3 (Invented) Name of products evaluated via the centralised procedure

Medicinal products authorised via the centralised procedure will have the same name across the Community. The name of the medicinal product may be either an invented name, or a common name or scientific name accompanied by a trademark or the name of the Marketing Authorisation Holder

To ensure that the proposed name of the product is acceptable for all Member States and does not create a public-health concern or potential safety risks, the EMEA/CHMP has set up a group, the (Invented) Name Review Group (NRG), to perform reviews of proposed invented names for medicinal products for human use.

In particular, the NRG checks that the proposed invented name
- does not convey misleading therapeutic or pharmaceutical connotations;
- is not misleading with respect to the composition of the product;
- is not liable to cause confusion in print, handwriting or speech with the invented name of an existing medicinal product.

For veterinary medicinal products, the CVMP is responsible for checking the proposed invented name according to the above criteria.

Provided that the medicinal product is eligible for evaluation under the centralised procedure, and where the applicant chooses to use an invented name for their medicinal product, the applicant should submit the proposed invented name(s) at the earliest 12 **months and at the latest 4 months** prior to the planned submission date of the marketing authorisation application.

When proposing an invented name, it is crucial that the applicant follows the EMEA guidelines (CPMP/328/98[82] and CVMP/328/98)[83] bearing in mind the paramount criteria of 'potential safety risk'.

Proposed invented names for medicinal products for human use are sent to every NRG contact point nominated by each EU-Member State (Norway and Iceland included), the European Commission (EC) and the World Health Organisation (WHO) for review. They are discussed at the NRG meeting the following month, considering the objections , concerns and comments received on grounds of safety. The conclusions are presented to the subsequent plenary CHMP meeting, after which the applicant is informed of the

---

[79] 'CHMP Rapporteur/Co-Rapporteur appointment : principles, objective criteria and methodology' (EMEA/124066/2005) http://www.emea.eu.int/pdfs/human/regaffair/12406605en.pdf

[80] 'Appointment and responsibilities of rapporteur and co-rapporteur for procedures regarding veterinary medicinal products' (EMEA/CVMP/928/02) http://www.emea.europa.eu/pdfs/vet/regaffair/092802en.pdf

[81] http://www.emea.europa.eu/htms/aboutus/experts.htm

[82] CHMP Guideline on the acceptability of invented names for human medicinal products processed through the centralised procedure (CPMP/328/98) http://www.emea.europa.eu/pdfs/human/regaffair/032898en.pdf

[83] CVMP Guideline on the acceptability of invented names for veterinary medicinal products processed through the centralised procedure (CVMP/328/98) at http://www.emea.europa.eu/pdfs/vet/regaffair/032898enfin.pdf

© EMEA 2009

outcome. For veterinary medicinal products invented names are sent to every contact point nominated by each EU-Member State (Norway and Iceland included) for review. Objections are then discussed at the following CVMP meeting, after which the applicant is informed of the outcome.

6.4 EMEA contact point in the centralised procedure

An **EMEA 'Product Team'** is set up for each human medicinal product intended to be submitted through the centralised procedure. The Product Team consists of a **Product Team Leader (PTL)** and Product Team Members (PTM) nominated by the EMEA. For veterinary products there is a single **Project Manager (PM)** for each product. The applicant is notified of the appointed PTL or PM. The product team or project manager is responsible for handling all procedural aspects of the application, both in the pre- and post-authorisation stage.

The PTL or PM, in co-operation with the Rapporteur and Co-Rapporteur, will ensure that the applicant is kept informed of all issues relating to the application. The PTL or PM will serve as the main liaison person between the EMEA, the Rapporteur, the Co-Rapporteur and the applicant.

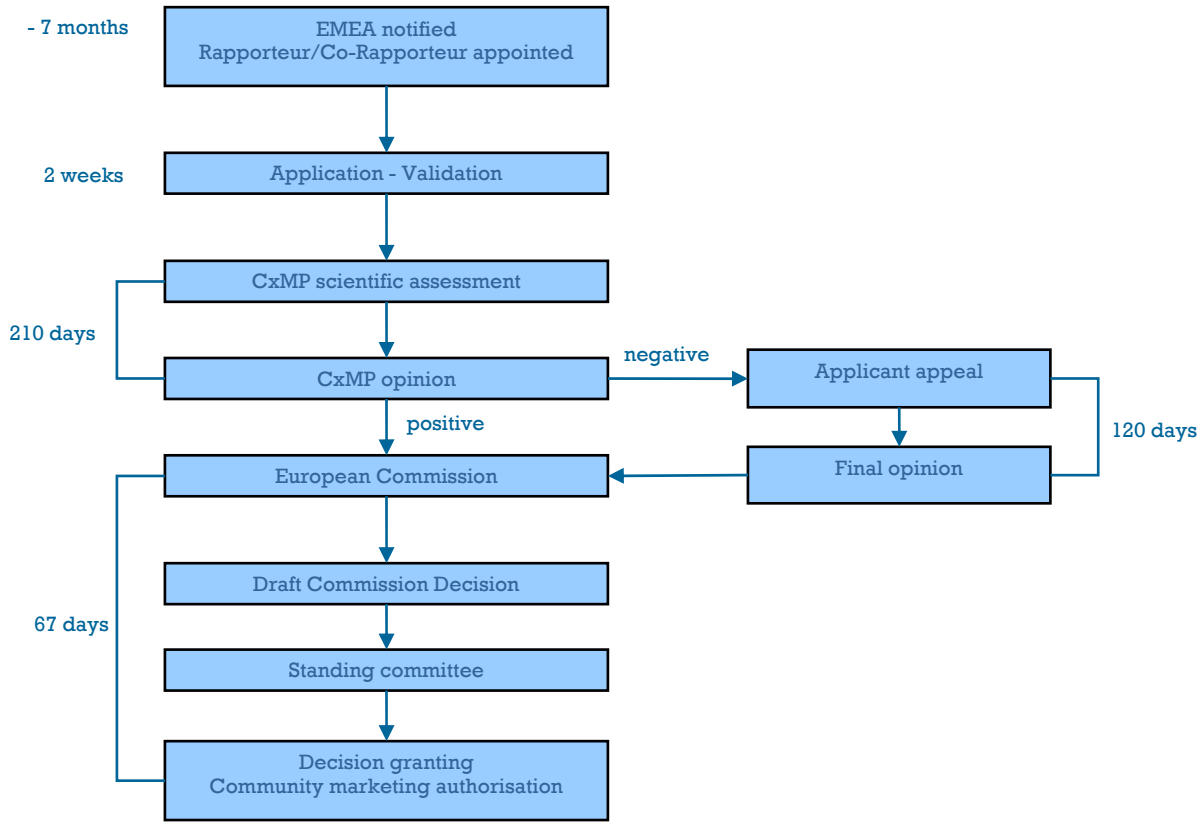


Figure 2 - Overview of the centralised procedure

6.5 EMEA Pre-Submission Meeting

When preparing the submission of a marketing authorisation application, applicants have the opportunity to meet the EMEA to discuss procedural or regulatory issues in relation to the upcoming submission, and to establish contacts with the EMEA staff that will be involved with the application. Experience has shown the usefulness of these "pre-submission meetings", even where the applicant has experience with the centralised procedure. Applicants are therefore strongly advised to request such a meeting .

Guidance on Pre-Submission Meetings with the EMEA can be found on the EMEA website[84].

Pre-Submission Meetings should take place approximately **6-7 months** prior to the anticipated date of submission of the application.

Requests for Pre-Submission Meetings should be sent to the EMEA using the 'pre-submission meeting request form' which is included in the EMEA pre-submission guidance[85] on the EMEA website.

6.6 Compilation of the application dossier

As explained in Section 1.3, data generated from pharmaceutical tests, non-clinical and clinical tests and trials with the medicinal product concerned, as well as other information required by the EU legislation, need to be provided to the EMEA and all CHMP members for evaluation.

The application dossier must be presented in accordance with the **EU-CTD (Common Technical Document)** presentation outlined in Volume 2B of the Notice to Applicants[86] published on the Commission website. The CTD is an internationally agreed format for the preparation of a well-structured application to be submitted to regulatory authorities in the three ICH (International Conference on Harmonisation) regions of Europe, USA and Japan. The CTD gives no information on the content of a dossier, but provides for a harmonized format of presentation of the necessary data to support the application in accordance with the legal/scientific requirements of each region.

The EU-CTD is organised in five modules: module 1 contains the specific EU administrative and prescribing information. The structure of modules 2, 3, 4, and 5 is common for all regions and will contain the high level summaries and quality, non-clinical and clinical documentation respectively.

For veterinary medicinal products the application dossier should be presented in accordance with Volume 6B of Notice to Applicants[87] published on the Commission website.

For the product information (SmPC, labelling and package leaflet texts), the EMEA provides the applicant with a template of what must be included in these documents. These templates for human and veterinary medicines are available on the EMEA website[88].

All applications need to be submitted in **English**. Detailed information on the number of copies required to be submitted to the EMEA, (Co-) Rapporteur, and CHMP/CVMP members are given in the EMEA pre-submission guidance[89] on the EMEA website.

---

[84] EMEA Guidance for Pre-submission Meetings for initial marketing authorisation applications for human medicinal products in the centralised procedure (EMEA/382712/2006)
http://www.emea.europa.eu/htms/human/presub/38271206en.pdf

[85] http://www.emea.europa.eu/ – Human Medicines (Veterinary Medicines) - Application Procedures - 'Pre-Submission Guidance'

[86] Volume 2B of the rules governing medicinal products in the European Union
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/index.htm

[87] Volume 6B of the rules governing medicinal products in the European Union
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/index.htm

[88] http://www.emea.europa.eu/ – Human Medicines (Veterinary Medicines) - Application Procedures - Product Information Templates

[89] http://www.emea.europa.eu/ – Human Medicines (Veterinary Medicines) - Application Procedures - 'Pre-Submission Guidance'

© EMEA 2009

For medicinal products for human use, the EMEA plans to implement electronic-only submission of applications for marketing authorisation with electronic Common Technical Document (e-CTD) as the required format. The EMEA currently accepts electronic only submissions in e-CTD or another format. From July 2009 use of e-CTD format will be strongly recommended by the Agency[90].

6.7 Submission and validation of the application dossier

The date and time of delivery of the dossier to the EMEA should be arranged between the applicant and the EMEA. Target dates for submission for human[91] and veterinary medicinal products[92] are published on the EMEA website.

If the original indicated submission date cannot be met, the applicant should immediately inform the EMEA, Rapporteur and Co-Rapporteur. A delayed submission can have consequences for already planned activities of the assessment teams of the Rapporteurs and Co-Rapporteurs.

The EMEA will check if the application meets all relevant legal (procedural) EU requirements ('validation'), before the start of the scientific evaluation. The EMEA will issue an invoice on the date of the notification of the administrative validation to the applicant, and fees will normally be payable within 45 days of the date of the said notification. For SME applicants, a deferral of the fee payment may be granted (see Section 2.3)

6.8 Evaluation of the application

Once the application is validated, the EMEA starts the evaluation procedure at the monthly starting date published on the EMEA website. The EMEA will ensure that the **evaluation is finalised within 210 days** (less any clock-stops for the applicant to provide a response to questions from the CHMP/CVMP).

The procedure can be **summarised** as follows:

In the first evaluation phase, the Rapporteur and Co-Rapporteur prepare assessment reports on the application within 80 days (85 days for veterinary products). The assessment reports are sent to all other CHMP/CVMP members for comment. Following discussion of the assessment reports, the CHMP/CVMP usually adopts a "list of questions", identifying 'major objections' and/or 'other concerns', which will be sent to the applicant by day 120. The Rapporteur and Co-Rapporteur then assess the applicant's response (second evaluation phase), submit them for discussion to the CHMP/CVMP and, taking into account the conclusions of this debate, prepare a final assessment report which also includes the draft SmPC, labelling and package leaflet. Once the evaluation is completed within the 210 days, the CHMP/CVMP adopts a favourable or unfavourable opinion on whether to grant the authorisation.

A more detailed **standard timetable** for the evaluation of an application in the centralised procedure is provided below:

DAY	ACTION
1	Start of the procedure
80 (85 Vet)	Receipt of the assessment report(s) from Rapporteur and Co-Rapporteur(s) by CHMP/CVMP members and EMEA.
100	Rapporteur, Co-Rapporteur, other CHMP/CVMP members and EMEA receive comments from members of the CHMP/CVMP.

[90] http://esubmission.emea.europa.eu/
[91] http://www.emea.europa.eu/htms/human/submission/submission.htm
[92] http://www.emea.europa.eu/ – Veterinary Medicines – Regulatory Guidance - 'Pre-Submission Guidance'

© EMEA 2009

115	Receipt of draft list of questions (including the CHMP/CVMP recommendation and scientific discussion) from Rapporteur and Co-Rapporteur.
120	CHMP/CVMP adopts the list of questions as well as the overall conclusions and review of the scientific data to be sent to the applicant by the EMEA. Clock stop.

The applicant is expected to respond within the timeframe agreed by the CHMP/CVMP from the date of receipt of the questions, which is usually 3 months for human medicinal products. Applicants may request an additional 3-month period by writing to the CHMP chairman outlining their reasons. For veterinary procedures the standard time frame for response is 6 months, which may be extended upon justified request. If the applicant is unable to respond within the time frame, then careful consideration should be given to withdrawing the application and resubmitting, if necessary after obtaining scientific advice, when the full information is available.

Further guidance on the response time for procedures relating to human medicinal products is provided in the EMEA guidance (EMEA/75401/06)[93] on the EMEA website.

DAY	ACTION
121	Submission of the applicant's responses, including revised SmPC, labelling and package leaflet texts in English. Restart of the clock.

After receipt of the responses, the following standard timetable applies:

DAY	ACTION
150 (160 Vet)	Joint response Assessment Report from Rapporteur and Co-Rapporteur received by CHMP/CVMP members and the EMEA.
170	Deadline for comments from CHMP/CVMP Members to be sent to Rapporteur and Co-Rapporteur, EMEA and other CHMP/CVMP Members.
180	CHMP/CVMP discussion and decision on the need to adopt a list of "outstanding issues" and/or an oral explanation by the applicant. If an oral explanation is needed, the clock is stopped to allow the applicant to prepare the oral explanation. Clock stop.

Applicants should normally respond (or prepare for an oral explanation) within one month. In exceptional circumstances a one, or maximum 2 months, extension may be granted if scientifically justified.

DAY	ACTION
181	Restart of the clock and oral explanation (if needed).

Information on how oral explanations are conducted (CPMP/2390/01)[94], is available on the EMEA website.

At the conclusion of the oral explanation, representatives of the applicant will be invited to leave and the CHMP/CVMP will discuss and provide a preliminary recommendation on the acceptability of the application. The applicant will be informed of the trend at CHMP/CVMP level at the end of the scientific discussion ahead of any formal vote to conclude the evaluation process.

[93] CHMP Guidance on 'Time allowed for applicants to respond to questions and issues raised during the assessment of new marketing authorisation applications in the centralised procedure' (EMEA/75401/06)
http://www.emea.europa.eu/pdfs/human/regaffair/7540106en.pdf
[94] 'Guidance to applicants on CPMP Oral Explanations in relation to centralised applications'(CPMP/2390/01)
http://www.emea.europa.eu/pdfs/human/regaffair/239001en.pdf

© EMEA 2009

DAY	ACTION
By 210	Adoption of CHMP/CVMP Opinion + CHMP/CVMP Assessment Report (and timetable for the provision of product information translations)

The EMEA will prepare a "Summary of Opinion" (for favourable as well as unfavourable opinions) in liaison with the applicant. Such summaries will be published on the EMEA website[95] after the adoption of the CHMP/CVMP Opinion.

If an applicant decides to **withdraw** its application before an opinion is adopted, the EMEA will make this public on its website together with the relevant assessment report.

6.9 Re-examination of the CHMP/CVMP opinion

The applicant may notify the EMEA/CHMP/CVMP in writing of their intent to request a re-examination of the CHMP/CVMP opinion within 15 days of its receipt (after which if such a request is not made, the opinion becomes final). The detailed grounds for the request must be forwarded to the EMEA within 60 days after receipt of the opinion.

Within 60 days from the receipt of the detailed grounds for re-examination, the CHMP/CVMP will re-examine its opinion and adopt a final opinion on the application. If considered necessary, an oral explanation can be held within this 60 days timeframe. No clock-stops apply to this procedure.

For further guidance on the re-examination procedure for human medicinal products and CHMP timetable for assessment (EMEA/CHMP/50745/2006)[96], refer to the EMEA website.

6.10 Decision-making process

After adoption of the CHMP/CVMP opinion, the EMEA has 15 days to forward its (final) opinion to the Commission. This is the start of the "decision-making process", whereby the CHMP/CVMP Opinion will be turned into a legally binding Commission decision for all Member States and the applicant.

The Commission decision granting a marketing authorisation to the medicinal product concerned includes the agreed SmPC, conditions for use, labelling and package leaflet texts (product information). The Commission decision is legally binding on all Member States, the product information must, therefore, be provided in all Community languages. The translations of the product information are normally provided by the applicant five days after adoption of the CHMP/CVMP Opinion. For SME applicants, the EMEA will provide for the translations of the product information. The translations will be reviewed by the Member States before transmission to the Commission.

Further details on the handling of translations (EMEA/5542/02)[97] are available on the EMEA website.

During the decision-making process, the Commission services check that the marketing authorisation complies with Community law, consulting various Commission directorates-general. In addition, the Commission consults the Standing Committee, which consists of representatives of all EU Member States. The opinion of the Standing Committee will normally be given by written procedure.

---

[95] http://www.emea.europa.eu/ – Human Medicines (Veterinary Medicines) - 'Summaries of Opinion'

[96] 'Guideline on the procedures for re-examination of CHMP opinions' (EMEA/CHMP/50745/2005) http://www.emea.europa.eu/pdfs/human/euleg/5074505en.pdf

[97] 'New linguistic review process of product information in the centralised procedure' (EMEA/5542/02) http://www.emea.europa.eu/ – Human Medicines (or Veterinary Medicines) - Application procedures – Quality Review of Documents - Product Information Templates - reference documents

© EMEA 2009

The Commission prepares a draft Commission decision within 15 days. Member States have 22 days to forward their written observations on the draft decision to the Commission. Within this time-limit, Member States must inform the Commission whether they approve the draft, reject it, or abstain. Any Member State failing to respond within the time-limit to express its opposition or intention to abstain from voting is deemed to have approved the draft.

The Commission will take a final decision within 15 calendar days after the end of the Standing Committee phase. The decision will be sent to the applicant and published in the EU official journal.

The Community marketing authorisation for the medicinal product will be granted in **67 days after adoption** of the final CHMP/CVMP opinion.

Once the Community marketing authorisation is granted, the EMEA will publish the CHMP/CVMP assessment report on the medicinal product which includes the reasons for its opinion in favour of granting authorisation, after deletion of any information of a commercially confidential nature. This document is called the **European Public Assessment Report (EPAR**). The EPAR includes a summary, in all EU languages, written in a manner that is understandable to the public. EPARs and their summaries are published on the EMEA website[98].

A marketing authorisation for a medicinal product is generally valid for five years. There is an exception when a conditional marketing authorisation for human medicinal products has been granted (see Section 6.11.2). The marketing authorisation may be renewed after five years on the basis of a re-evaluation by the EMEA/CHMP/CVMP of the benefit-risk balance of the product, upon application by the holder at least six months before expiry.

6.11 Early access to the EU market

6.11.1 Accelerated Assessment

In order to meet the expectations of patients as well as animal owners and to take account of the increasingly rapid progress of science and therapies, it is possible to obtain a marketing authorisation via an 'accelerated assessment procedure' (that is, within up to **150 days instead of 210 days**) for products which are of major public or animal health interest, in particular from the viewpoint of therapeutic innovation.

The applicant should notify their intent to request an accelerated assessment procedure as part of the "letter of intent" (see Section 6.1). The request itself for accelerated assessment can be submitted any time prior to the submission of the marketing authorisation application. The applicant's request needs to be duly substantiated. It should be sent to the PTL, (Co-) Rapporteur and all CHMP members for human products and to the PM, (Co-) Rapporteur and all CVMP members for veterinary medicinal products.

For further details on the documentation required to substantiate a request for accelerated assessment, and on the reduced timetable, refer to the EMEA guidance on the procedure for accelerated assessment for human medicinal products (EMEA/419127/05)[99] and veterinary medicinal products (EMEA/32995/06)[100] published on the EMEA website.

---

[98] http://www.emea.europa.eu/ Human Medicines (or Veterinary Medicines) - EPARs for authorised medicines

[99] CHMP 'Guideline on the procedure for Accelerated Assessment pursuant to Article 14 (9) of Regulation (EC) No 726/2004' (EMEA/419127/05) http://www.emea.europa.eu/pdfs/human/euleg/41912705en.pdf

[100] CVMP 'Guideline on the procedure for Accelerated Assessment pursuant to Article 39 (8) of Regulation (EC) No 726/2004' (EMEA/32995/06) http://www.emea.europa.eu/pdfs/vet/regaffair/3299506en.pdf

© EMEA 2009

6.11.2 Conditional Marketing Authorisation (human medicines only)

In addition to 'accelerated assessment', In order to meet unmet medical needs of patients and in the interests of public health, the CHMP can recommend the grant of marketing authorisations on the basis of less complete data than is normally required. In such cases, the granting of a marketing authorisation is **subject to certain specific obligations** to be reviewed annually ('conditional marketing authorisation').

This may apply to medicinal products used in seriously debilitating or life-threatening diseases, emergency situations in response to public health threats, or products designated as orphan medicinal products.

A conditional marketing authorisation can be granted where the CHMP finds that, although comprehensive clinical data referring to the safety and efficacy of the medicinal product have not been supplied, all of the following requirements are met:

- the risk-benefit balance of the medicinal product is positive;
- it is likely that the applicant will be in a position to provide comprehensive clinical data;
- unmet medical needs will be fulfilled;
- the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required.

Conditional marketing authorisations are **valid for one year**, on a renewable basis. The holder will be required to complete ongoing studies or to conduct new studies to confirm that the risk-benefit balance is positive. In addition, specific obligations may be imposed in relation to the collection of pharmacovigilance data.

The granting of a conditional marketing authorisation allows medicines to reach patients with unmet medical needs earlier than might otherwise be the case, and ensures that additional data on a product are generated, submitted, and assessed.

For further guidance on the criteria for conditional marketing authorisation, justifications to be provided and the procedure to be followed, refer to the implementing Commission Regulation (EC) No 507/2006 [101] on the Commission website and to guidance (EMEA/509951/2006) published on the EMEA website[102].

6.11.3 Marketing Authorisation under Exceptional Circumstances

In exceptional circumstances, a marketing authorisation can be granted subject to a requirement for the applicant to introduce **specific procedures, in particular concerning the safety** of the product ('marketing authorisation under exceptional circumstances'). Continuation of the authorisation will be linked to the annual reassessment of these procedures.

This can apply in cases where the applicant can show that it is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because:

---

[101] *Official Journal L 92, 30/3/2006 p. 6 – 9*

[102] 'Guideline on the scientific application and the practical arrangements necessary to implement Commission Regulation (EC) No 507/2006 on the Conditional Marketing Authorisation for Medicinal Products for Human Use falling within the scope of Regulation (EC) No 726/2004' (EMEA/509951/2006)
http://www.emea.europa.eu/pdfs/human/regaffair/50995106en.pdf

© EMEA 2009

- the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, or
- in the present state of scientific knowledge, comprehensive information cannot be provided, or
- it would be contrary to generally accepted principles of medical ethics to collect such information.

For further guidance on the conditions and procedures for the granting of a marketing authorisation under exceptional circumstances, refer to the EMEA guidance for human medicinal products (EMEA/357981/2005)[103] published on the EMEA website.

6.12 Marketing of the medicinal product in the Community

The marketing authorisation holder is legally obliged to inform the EMEA of the dates of the actual marketing of the product in the respective Member States, taking into account the various presentations authorised. Marketing authorisation holders must also notify the EMEA if the product, or any of its presentations, ceases to be marketed in any of the Member States, either temporarily or permanently. Such notification should normally be notified to the EMEA no less than two months before the marketing interruption.

Any authorisation, which is not followed by the **actual marketing in at least one Member State in the Community within three years** after authorisation, will cease to be valid (so-called sunset clause). Similarly, when a product previously marketed in the Community is no longer actually present on the market of any of the Member States of the Community for three consecutive years, the authorisation will cease to be valid. However, the Commission in exceptional circumstances may grant exemptions from these provisions on duly justified public health grounds.

For more details on this provision, refer to the 'list of questions and answers' on this topic included in the EMEA post-authorisation guidance[104] on the EMEA website.

6.13 Risk management and pharmacovigilance

Pharmacovigilance, or the surveillance of the safety of a medicinal product during its life on the market, is extensively regulated by EU directives and regulations. EU legislation requires Member States to establish national pharmacovigilance systems to collect and evaluate information on adverse reactions to medicinal products or their side effects and to take appropriate action where necessary. It also requires marketing authorisation holders to report suspected adverse reactions to the authorities in certain formats and within specified timeframes. Applicants and marketing authorisation holders are also required to provide Competent Authorities with a description of the pharmacovigilance system and, where appropriate, of the risk management system.

When a medicinal product is first authorised, the information available comes from experience in non clinical testing and clinical trials. During the evaluation its potential risks are weighed with its potential benefits based on what is known about the medicinal product at that time. Once it is placed on the market and used in a wider population, more information on its benefits and risks becomes available. Pharmacovigilance systems are designed to collect and continuously evaluate this information. If a medicinal product's overall risk/benefit profile changes significantly for any reason, it may become necessary to vary, withdraw or suspend its use.

---

[103] 'Guideline on procedures for the granting of a marketing authorisation under exceptional circumstances, pursuant to artcile 14(8) of Regulation (EC) No 726/2004' http://www.emea.europa.eu/pdfs/human/euleg/35798105en.pdf

[104] http://www.emea.europa.eu/ – Human Medicines - Application Procedures - 'Post-Authorisation Guidance'

© EMEA 2009

The reporting obligations of the various stakeholders are defined in the legislation, in particular Regulation (EC) No 726/2004, Directive 2001/83/EC as amended and Directive 2001/20/EC. In this light, a data processing network and management system for reporting and evaluating suspected adverse reactions during the development and following the marketing authorisation of medicinal products in the European Economic Area (EEA), named "EudraVigilance" database[105], was launched in December 2001. Eudravigilance is a powerful tool for the EMEA and national Competent Authorities in monitoring the safety of medicinal products and in minimising potential risks related to suspected adverse reactions. Taking into account the pharmacovigilance activities in the pre- and post- authorisation phase, EudraVigilance provides two reporting modules:

- **The EudraVigilance Clinical Trial Module (EVCTM)** to facilitate the electronic reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs) as required by Directive 2001/20/EC.
- **The EudraVigilance Post-Authorisation Module (EVPM)** designed for post-authorisation Individual Case Safety Reports (ICSRs), Regulation (EC) No 726/2004, Directive 2001/83/EC as amended, and Volume 9 of the "Rules Governing Medicinal Products in the European Union".

Volume 9a of the rules governing medicinal products in the European Union[106] should be consulted for further information on general pharmacovigilance requirements for medicinal products for human and veterinary use and in particular for guidance on the requirements and format for the description of a pharmacovigilance system, monitoring of pharmacovigilance obligations and pharmacovigilance inspections[107].

When an applicant submits a marketing application for certain types of products, a description of the risk management system may need to be submitted in the dossier. This should be submitted in the form of an EU Risk Management Plan (EU-RMP). The EU-RMP is a stand-alone document which summarises what is known about the safety of the product and discusses how the applicant/marketing authorisation holder will monitor and investigate further the safety profile of the product, and manage the risks associated with it. An EU-RMP (or an update if one already exists) may also need to be submitted with certain variations to an existing marketing authorisation. Once a product has an EU-RMP it needs to be updated throughout the life-cycle of the product.

Guidance on the risk management system, its description in the form of an EU Risk Management Plan (EU-RMP)and details of when this needs to be submitted is published in the'Guideline on risk management systems for medicinal products for human use' in Volume 9a of the rules governing medicinal products in the European Union [2]. A template for an EU-RMP is also available (EMEA/192632/2006) [108]. It is strongly recommended that discussions with the Competent Authorities on the need for, and content of, an EU-RMP should take place in advance of submission[109].

---

[105] Eudravigilance website: http://eudravigilance.emea.europa.eu/human/index.asp

[106] Volumes 9 of the rules governing medicinal products in the European Union http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/

[107] The guidelines on monitoring of compliance with pharmacovigilance regulatory obligations and pharmacovigilance inspections' are included for human products in Volume 9A of the rules governing medicinal product in the European Union (chapter 2) and Volume 9B for veterinary products (as a stand alone document)

[108] 'Annex C : Template for EU Risk Management Plan (EU-RMP)' (EMEA/192632/2006)

[109] For further information: http://www.emea.europa.eu/– Human Medicines (Veterinary Medicines) - Application Procedures - 'Pre-Submission Guidance'

© EMEA 2009

7. Other useful Information

7.1 Information on medicinal products

The Community Register of medicinal products [110] is published on the European Commission's website and contains a list of all medicinal products for human and veterinary use authorised via the centralised procedure and all designated orphan medicinal products for human use.

The EMEA's website contains a vast array of additional product information that may interest SMEs, including:

- Public summaries of opinions for orphan designation[111]
- CHMP & CVMP summaries of opinion[112]
  Note: The summary of opinion is replaced by the European Public Assessment Report (see below) once the European Commission has taken its decision granting or refusing a marketing authorisation.
- European public assessment reports (EPARs)[113]
- Maximum residue limits (MRL) summary opinions[114]
- Information on marketing authorisation and marketing authorisation application withdrawals[115]
- Product safety announcements[116]
- Product opinions for non-EU use[117]
- List of referred applications[118]

[110] http://ec.europa.eu/enterprise/pharmaceuticals/register/index.htm
[111] http://www.emea.europa.eu/htms/human/orphans/opinions.htm
[112] http://www.emea.europa.eu/ – Human Medicines (or Veterinary Medicines) - 'Summaries of Opinion'
[113] http://www.emea.europa.eu/ – Human Medicines (or Veterinary Medicines) - 'EPARs (Marketing Authorisation)'
[114] http://www.emea.europa.eu/ – Veterinary Medicines - MRLs – 'MRL Summary opinions'
[115] http://www.emea.europa.eu/ – Human Medicines - 'Withdrawals' or http://www.emea.europa.eu/– Veterinary Medicines - 'Marketing authorisation withdrawals'
[116] http://www.emea.europa.eu/ – Human Medicines - 'Product safety announcements'
[117] http://www.emea.europa.eu/ – Human Medicines - 'Product opinions for non-EU use'
[118] http://www.emea.europa.eu/ – Human Medicines (or Veterinary Medicines) - 'Referrals'

© EMEA 2009

7.2 List of Abbreviations

ADI	Acceptable Daily Intake
ASMF	Active Substance Master File
ATMPs	Advanced Therapy Medicinal Products
AUC	Area under the curve
CEP	Certificate of Suitability
CHMP	Committee for Human Medicinal Products
COMP	Committee for Orphan Medicinal Products
CTD	Common Technical Document
CVMP	Committee for Veterinary Medicinal Products
EC	European Commission
EEA	European Economic Area
EMEA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMOs	Genetically Modified Organisms
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
INN	International Non-proprietary Name
ITF	Innovation Task Force
IVMPs	Immunological Veterinary Medicinal Products
MA	Marketing Authorisation
MRL	Maximum Residue Limit
MUMS	Minor Uses and Minor Species
NRG	(Invented) Name Review Group
NTA	Notice to Applicants
OECD	Organisation for Economic Co-operation and Development
PDCO	Paediatric Committee
PD/PK studies	Pharmacodynamics/Pharmacokinetic studies
PhEur	European Pharmacopoeia
PIP	Paediatric Investigation Plan
PM	Project Manager
PTL	Product Team Leader
PTM	Product Team Member
PUMA	Paediatric Use Marketing Authorisation
SAWP	Scientific Advice Working Party
SAWP-V	Scientific Advice Working Party – Veterinary
SME	Micro, Small and Medium sized Enterprises
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
VICH	International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
WHO	World Health Organisation

7.3 Contact points at the EMEA

SME Office

The SME office has been set up within the agency to address the particular needs of smaller companies. The office aims to facilitate communication with SMEs through dedicated personnel within the agency who will respond to practical or procedural enquiries, monitor applications, and organise workshops and training sessions for SMEs. Any comments on the content of this SME User Guide should also be forwarded to the SME office:

SME office contact point: E-mail: smeoffice@emea.europa.eu
Direct telephone: (44-20) 74 18 85 75/86 43
Fax: (44-20) 75 23 70 40

Advanced Therapies and Technologies

General queries relating to Advanced Therapies and Technologies can be sent to:

Innovation Task Force contact point: E-mail: ITFsecretariat@emea.europa.eu

Orphan Designation

Requests for further information on orphan designation applications and requests to set up a free pre-submission meeting should be sent to:

Orphan medicines contact point: E-mail: orphandrugs@emea.europa.eu

Scientific Advice

For queries relating to the procedure for scientific advice or to request a free pre-submission meeting, contact:

For medicinal products for human use: E-mail: ScientificAdvice@emea.europa.eu
For medicinal products for veterinary use: E-Mail: vetscientificadvice@emea.europa.eu

Documentation services

A wide range of documents is published by the EMEA, including press releases, general information documents, annual reports and work programmes.
These and other documents are available:

- on the Internet at www.emea.europa.eu
- by email request to info@emea.europa.eu
- by fax to (44-20) 7418 8670
- by writing to the:

EMEA Documentation service
European Medicines Agency
7 Westferry Circus, Canary Wharf
London, E14 4HB
UK

© EMEA 2009

Annex 1

National provisions for SMEs applicable to the pharmaceutical sector

National provisions for SMEs applicable to the pharmaceutical sector
Last update April 2009

Country	Human & Veterinary medicines	National competent authority	CONTACT POINT	EXISTING NATIONAL PROVISIONS FOR SMES APPLICABLE TO PHARMACEUTICAL SECTOR
Austria	Human & Vet	AGES PharmMed LCM LCM Schnirchgasse 9 1030 Vienna Austria www.ages.at	Information on fee reductions for: Veterinary medicinal products: Mag. Eugen Obermayr Tel: +43 50 55 53 66 70 e-mail: eugen.obermayr@ages.at Medicinal products produced in pharmacies: Mag. Helga Lacina Tel: +43 50 55 53 66 40 e-mail: helga.lacina@ages.at	No specific provisions for SMEs applicable to pharmaceutical sector. There are general provisions for fee reductions for the authorisation and life-cycle management for veterinary medicinal products and medicinal products produced in local pharmacies. More detailed information about the Austrian fee levels is available on the Agency's website[119].
Belgium	Human & Vet	Agence Fédérale des Médicaments et des Produits de Santé 40 Place Victor Horta, Boite 40 1060 Brussels Belgium www.health.fgov.be	Contact point: Tel: +32 25 24 71 11 e-mail: info.dgm@fagg-afmps.be	No specific provisions for SMEs applicable to pharmaceutical sector. In the future there will be the possibility to have assistance for applications for specific medicinal products, for example, those for the treatment of minor species.

[119] Information on AGES PharmMed fees (currently only in German): http://www13.ages.at/servlet/sls/Tornado/web/ages/content/BAEE41BA96D77223C12570D5002C02C3

Bulgaria	Human	Bulgarian Drug Agency 26 Yanko Sakazov Blvd. 1504 Sofia Bulgaria www.bda.bg	Contact point: Tel: +359 29 43 40 46 e-mail: bda@bda.bg	The new amended national project of Law on the Medicinal Products in Human Medicines includes measures targeting small and medium sized enterprises.
	Vet	National Veterinary Service 15A 'Pencho Slaveykov'Blvd 1606 Sofia Bulgaria	Contact point: Dr Krasimir Zlatkov 'Control of VMP and Feeds Safety' Department Head of Department Tel: +359 29 15 98 69 Fax: +359 29 15 98 69 krasimir.zlatkov@nvms.government.bg	No specific provisions for SMEs applicable to veterinary pharmaceutical sector.

Cyprus	Human	Ministry of Health Pharmaceutical Services 7 Larnacos Avenue 1475 Lefkosia Cyprus http://www.moh.gov.cy	Contact point: Mr. Ioannis Kkolos Pharmaceutical Services, Tel: +357 22 40 71 32 e-mail: jkkolos@phs.moh.gov.cy	**Cyprus Research Promotion Foundation** The Cyprus Research Promotion Foundation is an independent establishment that promotes scientific and technological research in Cyprus. Its main measures include three packages: Measures on Health Research, Measures on SME Research and Measures Relating to the Development of Research Infrastructures. **Measures on Health Research** This scheme includes the program on "Biological Sciences-Health". The main target of this scheme is the design of high quality research in the fields of Public Health, Biomedical Sciences and Biotechnology and Food Science and Biotechnology. Grants under this scheme may be up to 160.000 Euros. **SME Research** This is a new scheme that includes the "Development of Research and Innovation in Businesses" program. The main aim of the scheme is to improve the competitiveness, viability and development of Cypriot enterprises and the creation of new work posts in research and development. Grants under this scheme may be up to 170.000 Euros. **Measures Relating to the Development of Research Infrastructures** The aim of the scheme is to help develop research infrastructures by upgrading current infrastructures and the creation of new ones with emphasis on innovative scientific sectors. Grants under this scheme may be up to 800.000 Euros. **Measures relating to research infrastructure** The provisions of Directive 2001/20/EC are fully transposed into the national legislation of Cyprus. Sponsors and investigators may utilise the current infrastructure to conduct paediatric clinical trials.

© EMEA 2009

	Vet	Athallassas 1471 Nicosia Cyprus	Contact point: Ioanna Talioti Veterinary Services 1417 Nicosia Cyprus Tel:+357 22 80 51 12 Email: italioti@vs.moa.gov.cy	Although, there are no specific provisions for fee reductions for SMEs, there are provisions for the reduction of fees included in the National Legislation [The VMPs (Fees) Regulations 132/2006]: "In the case of VMPs which are necessary for the Public Health and the volume of sales will not cover the expenses of their marketing, the Competent Authority may reduce the fees for the assessment and issue of the marketing authorisation or may not require any fees from the applicant."
Czech Republic	Human	State Institute for Drug Control Srobárova 48 100 41 Praha 10 Czech Republic www.sukl.cz	Contact point: Tel: +420 27 21 85 11 1 e-mail: sukl@sukl.cz	The Ministry of Health (MoH) has launched a call for proposals for the health programme of research and development of the MoH for the period of 2008-2011 including pharmacological research, focused on increase of treatment effectiveness and security and on enrichment and enhancement of the spectrum of medicines. The submitted applications are currently being evaluated. The MoH simultaneously prepares a follow-up programme for 2009-2011 which includes not only pharmacological but also paediatric research, focused on improvement of health care for young people, new therapeutic procedures and other contributions in the field of paediatric health care provision.
	Vet	Ústav pro státní kontrolu veterinárních biopreparátu a léciv Hudcova 56a 621 00 Brno - Medlánky Czech Republic www.uskvbl.cz	Contact point: Tel: 420 54 12 10 02 20 24 e-mail: uskvbl@uskvbl.cz	No specific provisions for SMEs applicable to veterinary pharmaceutical sector.

Denmark	Human & Vet	Danish Medicines Agency Axel Heides Gade 1 2300 Copenhagen Denmark www.dkma.dk	Contact point: Tel: +45 44 88 95 95 e-mail: dkma@dkma.dk	The national fee structure and service/administrative offers are adjusted to the fact that the national legislation is adapted to the special needs of Danish SME enterprises. In addition, fee exemptions are also available in specific circumstances e.g. that the medicinal product is essential to the patient treatment. For more detailed information about the Danish fee levels a total list of current fees charged in Denmark can be found on the Danish Medicines Agency website under the heading medicinal products, fees payable. In addition, the website contains information on how to obtain administrative and procedural assistance, and information about the supervision of medicinal products and medical devices, including possibilities to obtain scientific advice.
Estonia	Human & Vet	State Agency of Medicines 1 Nooruse Street 50411 Tartu Estonia www.sam.ee	Contact point: Tel: +372 73 74 14 0 e-mail: sam@sam.ee Mr. Lauri Maran Tel: +372 73 74 14 0 e-mail: lauri.maran@sam.ee	The Support of Enterprise and State Loan Guarantees Act (RT I 2003, 18, 96 as amended[120]) entered into force in Estonia on 1 May 2003 and contains some provisions for SMEs, applicable to the pharmaceutical sector. The Act sets out the bases, principles and organisation of state support for enterprises and the grant of state guarantees for loan agreements and leasing contracts.
Finland	Human	National Agency for Medicines P.O. Box 55 (Mannerheimintie 103b) 00301 Helsinki Finland http://www.nam.fi	Contact point: Tel +358 94 73 34 1	No specific provisions for SMEs applicable to human pharmaceutical sector.

[120] http://www.legaltext.ee/text/en/X70025K1.htm

	Vet	National Agency for Medicines P.O. Box 55 (Mannerheimintie 103b) 00301 Helsinki Finland http://www.nam.fi	_	No specific provisions for SMEs applicable to veterinary pharmaceutical sector.
France	Human	Agence française de sécurité sanitaire des produits de santé (Afssaps) 143-147 bd Anatole 93285 Saint-Denis CEDEX France www.afssaps.sante.fr	Contact point: Tel: +33 1 55 87 30 00 Mrs. Maisonneuve pascale.maisonneuve@afssaps.sante.fr	No specific provisions for SMEs applicable to human pharmaceutical sector Innovation task force, however, offers SMEs free and early scientific advice
	Vet	Agence Nationale du Médicament Vétérinaire AFSSA-ANMV La Haute Marche, BP 90203 35302 Javené Fougères France www.anmv.afssa.fr	Contact point: Tel: +33 2 99 94 78 78 e-mail: c.jourdan@anmv.afssa.fr	No specific provisions for SMEs applicable to veterinary pharmaceutical sector. But specific fees for marketing authorisation for MUMS and homeopathic veterinary medicinal products. Also, the annual fees take into account and is proportionate to the turnover of the company for each medicinal product. There is no fee where the turnover is less than 50000 euros and progressive annual fee until 1000000 euros (article D. 5141-60 of public health code)

Germany	Human	Federal Institute for Drugs and Medical Devices BfArM Kurt-Georg Kiesinger-Allee 3 53175 Bonn Germany www.bfarm.de	Contact point: Tel: +49 22 82 07 30 e-mail: info@bfarm.de Dr. Sabine Mayrhofer BfArM s.mayrhofer@bfarm.de Tel. +49 22 82 07 31 22	There is one specific provision aimed at SMEs presently implemented in Germany: the possibility for a reduction of fees for licensing activities. According to art. 3, para 2 of the German regulation on fees for the licensing of medicinal products, the fee can be reduced by up to 50 % if justified by the related operating expense of the authority on one hand and the relevance, economical value or other benefit for the applicant on the other hand.
	Human (sera, vaccines, blood preparations)	Paul Ehrlich Institut Bundesamt für Sera und Impfstoffe Paul Ehrlich Str. 51-59 63225 Langen Germany www.pei.de	Contact point: Tel: +49 61 03 77 20 01 e-mail: pei@pei.de Bettina Ziegele, M.A. Deputy Head Unit Management Support	The Paul-Ehrlich-Institut is in the process of establishing an SME Office. Information about the establishment of an SME Office with all necessary details will be published on the Paul-Ehrlich-Institut website in due course.
	Vet	Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL) Rochusstrasse 65 53123 Bonn Germany www.bvl.bund.de	Contact point: Tel: +49 22 86 19 80 e-mail: poststelle@bvl.bund.de Prof. Dr. Reinhard Kroker reinhard.kroker@bvl.bund.de	The German fee regulation offers the possibility to reduce the fee normally charged for a marketing authorisation to such a degree that only 25% of it has to be paid. However, this only applies to products for which the expenses outweigh the expected profit and public interest can be identified (no alternative) or which will be used in rare cases. If the authorisation is refused it is possible to refrain from charging a fee. There is no possibility for fee deferral according to German fee regulation.
Greece	Human & Vet	EOF – National Drug Organisation Mesogion Avenue 284 Holargos Athens 15562 Greece www.eof.gr	Contact point: Tel: +30 21 06 50 72 00 e-mail: relation@eof.gr	No specific provisions for SMEs applicable to pharmaceutical sector.

© EMEA 2009

Hungary	Human	National Institute of Pharmacy Zrínyi U. 3 1551 Budapest Hungary www.ogyi.hu	Contact point: Prof Tamás L Paál Tel: +36 18 86 93 20 E-Mail : tpaal@ogyi.hu	No specific provisions for SMEs applicable to pharmaceutical sector.
	Vet	Institute for Veterinary Medicinal Products Szállás utca 8 1107 Budapest 10.Pf. 318 Hungary www.ivmp.gov.hu	Contact point: Tel: +36 14 33 03 30 e-mail: info.aogyti@oai.hu Dr. Ernö Horvath horvathe@oai.hu	No specific provisions for SMEs applicable to pharmaceutical sector.
Ireland	Human & Vet	Irish Medicines Board The Earlsfort Centre Earlsfort Terrace Dublin 2 Ireland www.imb.ie	Information on fees is available from IMBwebsite: www.imb.ie Tel: 353 16 76 49 71 Email imb@imb.ie Specific queries on service item fees can be directed to accounts@imb.ie	No specific provisions for SMEs applicable to pharmaceutical sector. There is a service item fee (reduced fee) that relates to the market segment/use of the product (not to the size of the individual pharmaceutical company).

Italy	Human	Agenzia Italiana del Farmaco Via Sierra Nevada, 60 00144 Roma Italy http://www.agenziafarmaco.it	Contact point: Dott.ssa Silvia Fabiani s.fabiani@aifa.gov.it	No specific provisions for SMEs applicable to pharmaceutical sector, although assistance is available for promoting exports. General provisions exist, such as Law 297 (Financing of Industrial Research) which handles funds from FAS (the Fund for Underutilised Areas of the Ministry for Universities and Research) and foresees increased funding for SMEs compared to large companies, or tax credits for new research, grants and contributions to universities. In addition, within Law 46 of the Ministry for Development (Ministero dello Sviluppo) for the technical innovation and pre-competitive development, there are special provisions for SMEs.
	Vet	Piazzale Marconi 25 00144 Roma Italy www.ministerosalute.it	Contact point: Dr. Daniela Raneri d.raneri@sanita.it Tel: +39 06 59 94 37 34 Alternate: Dr. Virgilio Donini v.donini@sanita.it Tel: +39 06 59 94 65 90	No specific provisions for SMEs applicable to pharmaceutical sector.

Latvia	Human	State Agency of Medicines Jersikas iela 15 1003 Riga Latvia www.zva.gov.lv	Contact point: Ms. Ludmila Romanova tel: +371 67 07 84 44 e-mail: ludmila.romanova@zva.gov.lv	Although, there are no specific provisions for fee reductions for SMEs, the national fee structure is adjusted to the fact that Latvian enterprises fulfil SME definition. In addition, Latvia has rules to permit reduction of marketing authorisation costs in exceptional cases. The State Agency of Medicines is entitled to take a decision regarding the exemption for payment or reduction of payment for activities associated with evaluation, registration, re-registration of medicinal products if the medicinal products are substantially needed for the provision of medical treatment process, if the medicinal products are essentially necessary for ensuring treatment of rare diseases or are to be distributed in limited amounts.
	Vet	Zalu valsts agentura 15 Jersikas Street 1003 Riga LATVIA www.zva.gov.lv	Contact point as above	No specific provisions for SMEs applicable to pharmaceutical sector.
Lithuania	Human	State Medicines Control Agency Traku 14 01132 Vilnius Lithuania vvkt@vvkt.lt	Contact point: Mr. Mindaugas Buta Head of Medicines Safety and Information Unit E-mail: mindaugasbuta@vvkt.lt Tel: +370 52 63 90 53	Currently no specific provisions for SMEs applicable to pharmaceutical sector. There are some proposals for general provisions for fee reductions for the authorisation and life-cycle management of medicinal products under evaluating at governmental level

© EMEA 2009

	Vet	Lithuanian State Inspection on Veterinary Preparations Department of control of veterinary preparations J. Naujalio g. 21B 48332 Kaunas Lithuania www.lvvpi.lt	Contact point: Tel.: +370 37 26 74 55 Fax: +370 37 40 68 20 e-mail: lvvpi@lvvpi.lt Senior veterinary surgeon inspector Rolandas Dabašinskas Tel.: +370 37 36 01 37 e-mail: dabasinskas@lvvpi.lt	No specific provisions for SMEs applicable to pharmaceutical sector.
Luxembourg	Human & Vet	Direction de La Santé Villa Louvigny Division de la Pharmacie et des Medicaments Allée Marconi 2120 Luxembourg www.ms.etat.lu	Contact point: Tel: e-mail: Ministere-Sante@ms.etat.lu	No specific provisions for SMEs applicable to pharmaceutical sector.

Malta	Human	Medicines Authority Divizjoni Tas-Sahha Bezzjoni Ghar-Regolazzjoni Tal-Medicini 198 Rue D'Argens GZR 03 Gzira Malta www.medicinesauthority.gov.mt	Contact point: Tel: +356 23 43 90 00 e-mail: info.medicinesauthority@gov.mt Dr P. Vella Bonanno CEO - patricia.vella@gov.mt	In Malta companies engaged in the production of pharmaceuticals (including the packaging of such products) qualify for assistance under the business promotion Act/ Regulations - Article 3(1)(a) and Regulation 4(3)(a)(01). This is subject to an approval of the activity by Malta Enterprise - an entity responsible to bring Foreign Direct Investment to Malta and to aid businesses set up in Malta The main assistance is as follows: *Fiscal* - Investment allowance* under Article 7, equivalent to 50% or 20% of the value of investment in plant & machinery and industrial structures respectively; - Reduced Rates of Tax of 5% or 10% up to year of assessment 2009, subject to a capping vis a vis employment (regulation 43); - Investment Tax Credit* equivalent to (as from January 2007) 30% (large), 40% (medium) and 50% (small) of the value of investment or the value of wages (24 months) of jobs created as a result of an investment project. Present % rates - 50% Large and 65% SMEs *Non Fiscal* - Soft loan* - Regulation 8; - Loan interest subsidies* - Regulation 9 - Loan Guarantees* - Regulation 10 - Training Grants - Regulation 14 - Gozo Transport Grant - Article 23 (for companies operating from Gozo) *Subject to Regional State Aid Intensity Levels - Incentives under LN 335 - Income Tax Act - Tax credit for Wages and Tuition Expenditure: Tax credit covering 17.5% of the costs that companies incur by way of wages and course costs, in sponsoring their employees for an approved general or specific qualification.

© EMEA 2009

	Vet	Ministry for Food, Agriculture and Fisheries (Malta) Albertown CMR 02 Marsa Malta	-	No specific provisions for SMEs applicable to veterinary pharmaceutical sector.
The Netherlands	Human & Vet	College ter Beoordeling van Geneesmiddelen Medicines Evaluation Board Kalvermarkt 53 P.O.Box 16229 2511CB Den Haag The Netherlands www.cbg-meb.nl	Contact point: Tel: +31 70 35 67 40 0 e-mail: info@cbg-meb.nl	No specific provisions for SMEs applicable to pharmaceutical sector, with the exception of fee reduction or deferral of the fee for registration of a medicine. In addition, at present, there is no fee payable for scientific advice.
Poland	Human & Vet	Office for Registration of Medicinal Products, Medical Devices and Biocidal Products 41 Zabkowska Str. 03-736 Warsaw Poland www.bip.urpl.gov.pl	Contact point: Tel: +48 22 49 21 10 0	No specific provisions for SMEs applicable to pharmaceutical sector.
Portugal	Human & Vet	INFARMED - Instituto Nacional da Farmácia e do Medicamento Parque da Saúde de Lisboa Avenido do Brasil, n° 53 1749-004 Lisboa Portugal www.infarmed.pt	Contact point: Tel: +35 21 79 87 10 0 e-mail: infarmed@infarmed.pt Ms. Sara Macedo sara.macedo@infarmed.pt	There is one specific provision aimed at SMEs presently implemented in Portugal: the System of Incentives to Small Entrepreneurial Initiatives (SIPIE). This incentive was created by Portaria no. 317-A/2000 of 31 May. SIPIE is a program that applies to all the economic sectors, including the pharmaceutical sector, through incentives given to specific projects. The above-mentioned program and project description can be found on the webpage of the Institute that supports SMEs in Portugal, the IAPMEI[121]

[121] IAPMEI website: http://www.iapmei.pt/index.php and specific information on SIPIE: http://www.iapmei.pt/iapmei-art-02.php?id=76&temaid=13

Romania	Human	National Medicines Agency 48, Av. Sanatescu 011478 Bucharest Romania www.anm.ro/home.html	Contact point: Mrs. Simona Raicu, PhD, Head of the Pharmaceutical Inspection Department simona.raicu@anm.ro Tel. : + 40 21 316 10 79 Fax: + 40 21 316 34 97	No specific provisions for SMEs applicable to human pharmaceutical sector.
	Vet	National Sanitary Veterinary and Food Safety Authority Str. Negostori nr.1 bis Sector 2 023951 Bucharest Romania	-	No specific provisions for SMEs applicable to veterinary pharmaceutical sector.
Slovak Republic	Human	State Institute for Drug Control Kvetná 11 825 08 Bratislava 2 Slovak Republic www.sukl.sk	Contact point: Tel: +42 1 2 50 70 11 11 e-mail: sukl@sukl.sk PhDr. Dana Vysko□ilová Public Relations Manager vyskocilova@sukl.sk	The Sate Institute for Drug Control offers administrative and procedural assistance to applicants upon request, in line with standard procedures and in accordance with the state drug policy. There are no fee waivers applicable specifically for SME applications.
	Vet	Institute for State Control of Veterinary Biologicals and Medicaments Biovetska 34 949 01 Nitra Slovak Republic www.uskvbl.sk	Contact point: Tel: +421 37 65 15 50 6 e-mail: uskvbl@uskvbl.sk	No specific provisions for SMEs applicable to pharmaceutical sector.

Slovenia	Human & Vet	Agency for Medicinal Products and Medical Devices of the Republic of Slovenia Mali trg 6 1000 Ljubljana Slovenia www.mz.gov.si	Contact point: Tel: +38 6 1 47 86 00 1 e-mail: gp.mz@gov.si Ms. Jelka Beltram Kovacic Jelka.Kovacic@gov.si	No specific provisions for SMEs applicable to pharmaceutical sector.
Spain	Human & Vet	Agencia Española del Medicamento y Productos Sanitarios Parque Empresarial Las Mercedes Edificio 8 C/Campezo 1 28022 Madrid España www.agemed.es	Contact point: Tel +34 91 82 25 02 8 e-mail: sgaem@agemed.es Ms. Cristina Avendaño	No specific provisions for SMEs applicable to pharmaceutical sector.
Sweden	Human & Vet	Medical Products Agency Dag Hammarskjölds väg 42 751 03 Uppsala Sweden www.lakemedelsverket.se	Contact point: Tel: +46 18 17 46 00 e-mail: registrator@mpa.se Ms. Ylva Satrell Ylva.Satrell@mpa.se	The Medical Products Agency has established a Regulatory Advice Office to assist especially small, new, national companies with regulatory queries although queries from all kind of companies are accepted.
United Kingdom	Human	Medicines and Healthcare products Regulatory Agency Market Towers 1 Nine Elms Lane London SW8 5NQ United Kingdom www.mhra.gov.uk	Contact point: Tel: +44 20 70 84 20 00 e-mail: info@mhra.gsi.gov.uk Ms. Sue Jones Policy Division sue.jones@mhra.gsi.gov.uk	The MHRA offers a number of easements to SMEs to aid their ability to pay the fee due. These easements include: - 25% of the application fee for a new active substance at the time of the application with the remaining 75% payable within 30 days of the marketing authorisation being determined; - 50% of most other marketing authorisation applications fee at the time of application and 50% within 30 days of the application being determined;

© EMEA 2009

				- 25% of the fee relating to outgoing mutual recognition applications for new active substances at time of application and 75% once that procedure has been completed; - 50% for most other outgoing mutual recognition applications and 50% once that procedure has been completed; - 50% at the time of applications for Manufacturers' or Wholesale Dealers' licences with 50% payable when the applications have been determined; The 50% 'rule' also applies to the payment of: - all inspection fees, including those relating to registrations for traditional herbal medicines; - applications for traditional herbal medicines registrations and applications for complex variations to traditional herbal registrations; - applications for registrations under the homeopathic registration schemes. In addition to these easements, there are some lower fees that reflect the size of a company. For example, wholesale dealers who deal meet certain criteria including low turnover of licensed products, are eligible for lower application, inspection and annual fees. Also the annual fees for marketing authorisations are set with a sliding scale relating to turnover of the product. The MHRA offer pre-application scientific advice meetings at which companies can seek advice on the development of a product, but there is currently no easement of payment for fees relating to these meetings.

© EMEA 2009

	Vet	Veterinary Medicines Directorate Woodham Lane New Haw Addlestone KT15 3LS United Kingdom www.vmd.gov.uk	Contact point: Tel: +44 93 23 36 91 1 e-mail: postmaster@vmd.defra.gsi.gov.uk Mr. Gavin Hall g.hall@vmd.defra.gsi.gov.uk	No specific provisions for SMEs in veterinary medicines legislation.

© EMEA 2009